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EDITORIAL

Our dear readers,

We are happy to publish the second issue of our journal for 2022 with 60 articles. Although COVID-19 pandemic is still goes on, we increase the scientific quality of our journal. First of all, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering indexes such as ESCI, PubMed and SCI-Expanded. I would like to thank all authors for submitting articles contributing to both domestic and international literature with their comprehensive scientific content for publication in our journal. We hope that this issue will be useful to our readers.

Sincerely yours

Assoc. Prof. Alpaslan TANOĞLU, MD
Editor-in-Chief

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Original Article

HEALTH SCIENCES
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Risk factors for chronic kidney disease progression in patients with solitary kidney

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ABSTRACT

Introduction: The prevalence of chronic kidney disease (CKD) is rapidly increasing worldwide. Solitary kidney is also increasing in ranking among the CKD etiologies, because there has been a rapid increase in the number of radical nephrectomies due to an increased number of renal transplantations from live donors and an increased number of patients with renal cell carcinoma. The aim of the current study is to identify risk factors that affect the glomerular filtration rate (GFR) in individuals with solitary kidney.

Material and Method: The current study included 204 patients (75 with congenital, 129 with acquired solitary kidney). Laboratory data during the first and last admissions were recorded. Patients divided into two groups according to annual decline of eGFR. Group I and II consisted of patients whose annual decline eGFR was more than 1ml/min/1.73 m² and less than 1ml/min/1.73 m², respectively. In addition, patients were divided into two groups as patients with congenital and acquired solitary kidney. The first control is the first examination in the nephrology outpatient clinic for congenital solitary kidney patient and the post-operative examination on the fourteenth day after discharge from the hospital for the acquired solitary kidney patient. The final control is the examination within the last three months before reaching the primary endpoint of the study.

Results: Of the patients, 36.8% were male, and the average age was 57.16±15.04 years. The duration of the follow-up period was 6.48±3.69 years. Group I had higher rates of diabetes mellitus, cardiovascular disease, older age, higher mean blood pressure(MBP), glucose, CRP, total cholesterol (TC), LDL-cholesterol, non-HDL-cholesterol, triglyceride/non-HDL-cholesterol ratio and lower albumin. In the group with acquired solitary kidney, the patients were older, the incidence of cardiovascular diseases was higher, and the eGFR at the first and last admission was lower. There was no difference between acquired SK and congenital SK in terms of annual change in eGFR. In regression analysis CRP, LDL-cholesterol, non-HDL-cholesterol, TG/non-HDL-cholesterol ratio are independent risk factors on annual decline of eGFR. Having a congenital or acquired single kidney had no effect on the annual decline of eGFR. In addition, TC, TC/HDL-cholesterol, triglyceride/non-HDL-cholesterol, triglyceride/HDL-cholesterol ratios, non-HDL -cholesterol correlated with CRP positively.

Conclusıon:Patients with solitary kidney have higher risk of developing CKD. Inflammation and dyslipidemia must be paid attention to protect eGFR. Besides the atherosclerosis in the microcirculation, dyslipidemia affect eGFR through inflammation. Having a congenital or acquired single kidney has no effect on the annual decline of eGFR.

Keywords: Solitary kidney, inflammation, dyslipidemia, proteinuria, glomerular filtration rate

INTRODUCTION

Chronic kidney disease (CKD) is an important public health problem worldwide. In spite of the variability among different societies and locations, the prevalence of CKD increases on average 6% per year (1). With time, patients with CKD experience deterioration in their quality of life. Moreover, CKD patients have a 10 to 20-fold increase in mortality due to cardiovascular diseases (CVD) compared to the normal population. This rate can be up to 30-times in cases developing end-stage renal disease (ESRD) (2,3). Therefore, it is very important to closely monitor patients at risk for developing ESRD.

Although diabetes mellitus (DM), hypertension (HT), and glomerulonephritis are the most common causes in CKD etiologies, solitary kidney has recently taken its place among CKD etiologies, because there is an increasing number of patients developing ESRD worldwide, there has also been an increase in the number of renal transplantations from live donors. Additionally, due to an increase in the number of patients with renal cell CA, there have also been increases in the number of partial and radical nephrectomies. In the past, studies revealed that there was no difference between live donors and the general population in terms of developing ESRD and mortality rates(4,5). However, more recent studies in the USA and Norway reported that the risk of developing ESRD was increased by 8 and 11 times, respectively, in live donors (6,7). Likewise, a 2019 Korean study indicated that the risk of developing CKD increased by 3.26 times in live donors compared to the control group (8).

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The aim of the current study is to identify risk factors that affect the glomerular filtration rate (GFR) in individuals with solitary kidney.

MATERIAL AND METHOD

The study was carried out with the permission of Clinical Research Ethics Committee of Ankara Training and Research Hospital (Date: 21.04.2020, Decision No: E-20/201). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

The study included 204 patients (75 with congenital solitary kidney and 129 with acquired solitary kidney) who were followed up with between 2005 and 2020. Patients between the ages of 18-80 and whose single kidney was shown radiologically were included in the study. Patients who needed intensive care due to complications in the postoperative period, had to use nephrotoxic agents, developed AKI, underwent dialysis, did not come for regular controls, and with partial nephrectomy or hypoplastic kidney, who had renal cell carcinoma with stage 2,3 or 4, other active malignancies, and chronic inflammatory disease were excluded from the study. The primary endpoint of current study was death or initiation of renal replacement therapy.

Laboratory Parameters

As well as demographic characteristics, serum urea, creatinine, and eGFR values, 24 h urine protein values at the first and last control, and complete blood count, albumin, CRP, total cholesterol (TC), HDL-cholesterol, LDL-cholesterol, non-HDL-cholesterol, and triglyceride levels at the first control were recorded. The first control is the first examination in the nephrology outpatient clinic for congenital solitary kidney patient and the post-operative examination on the fourteenth day after discharge from the hospital for the acquired solitary kidney patient. The final control is the examination within the last three months before reaching the primary endpoint of the study or the study end date.

GFR was calculated by the CKD-EPI (CKD Epidemiology Collaboration) equation. LDL-cholesterol was indirectly calculated using Friedewald formula. Non-HDL-cholesterol was calculated as HDL-cholesterol substracted from total cholesterol. Patients were classified according to anual change of eGFR as group I and II. Group I and group II consisted of patients whose annual decline of eGFR was more than 1 ml/min/1.73 m² and less than 1 ml/min/1.73 m², respectively. The annual decline of eGFR was calculated by the difference between baseline eGFR and the last eGFR divided by time interval in years. The annual decline in eGFR was grouped as above and below 1 ml/min/1.73 m² so that the groups were not affected by the decrease in EGFR after the age of fourty. Patients were also divided into two groups as patients with congenital and acquired solitary kidney.

Statistical Analyses

Analyses were conducted using SPSS (version 22.0). All data were fist checked for normality of distribution using the Kolmogrov-Smirnov and Shapirov-Wilk test. Normally distributed data are presented as the mean± standard deviation. Non-normally distributed data are represented as the median (inter-quartile range). Independent samples T test, was used to compare parametric continuous variables between groups. Mann Whitney U was employed for the comparison of non-parametric variables. Pearson's X^2 or Fisher's exact were used for categorical variables. Correlation analyses were performed using the Pearson /Spearman correlation coefficient. Univariate and multivariate cox regression analysis were used to identify independent risk factors on annual decline of eGFR. A significant difference was considered when $p<0.05$.

RESULTS

Of the patients, 36.8% were male, and the average age was 57.16±15.04 years. The duration of the follow-up period was 6.48±3.69 years, and 129 patients had nephrectomy. The causes of nephrectomy were nephrolithiasis (45.7%), renal mass (25.5%), unknown etiology (12.4%), donation (9.4%), infection (3.9%), and trauma (3.1%). Comparison of demographic characteristics between the two groups revealed that group I had higher rates of DM and cardiovascular disease, older age, and higher mean blood pressure values than group II. A difference between the groups according to the rates of congenital or acquired solitary kidney was not found. In addition, the incidence of proteinuria and eGFR values were similar at baseline. Compared to group II, group I had higher glucose, CRP, total cholesterol, LDL-cholesterol, non-HDL-cholesterol, triglyceride/non-HDL-cholesterol ratio and lower albumin (**Table 1**). In the group with acquired solitary kidney, the patients were older, the incidence of cardiovascular diseases was higher, and the eGFR at the first and last admission was lower. However, there was no difference in terms of annual change in eGFR (**Table 2**). In regression analysis CRP, LDL-cholesterol non-HDL-cholesterol, TG/non-HDL-cholesterol ratio are independent risk factors on annual decline of eGFR. Having a congenital or acquired single kidney had no effect on the annual decline of eGFR (**Table 3**). In addition, total cholesterol, total cholesterol/HDL-cholesterol, triglyceride/non-HDL-cholesterol, triglyceride/HDL-cholesterol ratios, and non-HDL-cholesterol correlated with CRP positively (**Table 4**).

Table 1. Comparison of basic characteristics and laboratory data between groups

Parameters	All patients (n:204)	Group I (n:123)	Group II (n:81)	P
Gender (Female) (%)	63.2	60.2	67.9	0.215
DM (%)	24.5	32.5	12.3	0.001
CVD (%)	12..7	17.1	6.2	0.002
HT (%)	67.2	70.7	61.7	0.325
Cause of SK Congenital (%)	36.8	34.1	40.7	0.456
Follow-up time (years)	6.48±3.69	7 (7) (min:0.5-max:21)	6 (5) (min:max:16)	0.521
Age (year)	57.16±15.04	63 (17) (min:22-max:80)	54 (23) (min:18-max:78)	<0.001
MBP (mmHg)	94.51±10.38	93 (19) (min:70-max:117)	93 (14) (min:73-max:120)	0.039
Urea at first admission (mg/dL)	39.47±17.9	36 (19) (min:17-max:112)	34 (18.5) (min:17-max:129)	0.321
Creatinine at first admission (mg/dL)	1.28±0.46	1.2 (0.56) (min:0.6-max:3.6)	1.18 (0.55) (min:0.7-max:2.45)	0.351
Proteinuria at first admission (mg/day)	324.75±766.71	100 (500) (min:100-max:4940)	100 (185) (min:100-max:1660)	0.444
EGFR atfirst admission (ml/min/1.73 m²)	63.42±53.74	57.1 (33.2) (min:12-max:76.1)	58 (32.3) (min:24-max:112)	0.412
Urea at last admission (mg/dL)	45.94±21.91	45 (26) (min:18-max:155)	34 (13.5) (min:17-max:66)	<0.001
Creatinine at last admission (mg/dL)	1.35±0.94	1.29 (0.64) (min:0.57-max:9.5)	0.96 (0.38) (min:0.58-max:1.77)	<0.001
Proteinuria at last admission (mg/day)	443.62±1087.95	100 (448) (min:100-max:6560)	100 (100) (min:100-max:3440)	<0.001
eGFR at last admission (ml/min/1.73 m²)	62.42±26.57	52 (29.2) (min:3-max:108)	80 (37.45) (min:34.9-max:127)	0.002
Annual change of eGFR (ml/min/1.73 m²)	0.49±9.74	-1.23 (0.482) (min:-44.2;max:+2.40)	4.07 (4.65) (min:+1.25;max:+43.6)	<0.001
Glucose (mg/dL)	109.26±31.65	99 (28) (min:72-max:250)	98 (17) (min:77-max:208)	0.023
Total Cholesterol (TC) (mg/dL)	193.06±48.57	195 (58) (min:95-max:409)	180 (58.5) (min:114-max:407)	0.011
HDL-cholesterol (mg/dL)	46.21±12.78	44 (13) (min:22-max:82)	45 (19.5) (min:19-max:89)	0.323
LDL-cholesterol (mg/dL)	113.11±34.21	116 (48) (min:50-max:224)	102 (42.5) (min:34-max:222)	0.014
Triglyceride (TG) (mg/dl)	176.64±110.54	156 (148) (min:48-max:640)	134 (80) (min:45-max:527)	0.546
TC/HDL-cholesterol ratio	4..42±1.5	4.46 (1.91) (min:2.2-max:9.74)	3..3 (1.76) (min:2.1-max:14)	0.016
LDL/HDL-cholesterol ratio	2.59±0.9	2.67±0.85 (min:0.95-max:5.96)	2.46±0.96 (min:0.33-max:5)	0.876
TG/HDL-cholesterol ratio	4.3±3.33	3..4 (4.12) (min:0.89-max:22.37)	3.13 (2.71) (min:0.79-max:21)	0.159
TG/non-HDL-cholesterol ratio	0.52±0.29	0.56±0.3 (min:0.1-max:1.35)	0.47±0.27 (min:0.19-max:1.32)	0.042
non-HDL-cholesterol (mg/dL)	146.85±47.31	151 (52) (min:65-max:367)	127 (59.5) (min:77-max:378)	0.002
Uric acid (mg/dL)	6.11±1.6	6.1 (2.5) (min:2.6-max:11.4)	5.9 (2.5) (min:2.6-max:9.8)	0.323
Albumin (g/dL)	4.32±0.42	4.3 (0.5) (min:3.1-max:5.29)	4.4 (0.42) (min:3.1-max:3.54)	0.036
CRP (mg/L)	1.93±2.12	1.1 (2.2) (min:0.2-max:15)	1 (1.5) (min:0.2-max:12)	0.006
WBC (10^6/L)	7722±2043	7500 (3200) (min:4100-12800)	7400 (2400) (min:3500-max:13300)	0.458
Neutrophil (10^6/L)	4832±1663	4600 (2300) (min:2000-max:9300)	4400 (1950) (min:1900-max:11400)	0.563
Lymphocyte (10^6/L)	2139±701	2100 (1100) (min:800-max:4310)	2000 (800) (min:800-max:4400)	0.741
Monocyte (10^6/L)	519±186	500 (200) (min:100-max:1070)	500 (200) (min:200-max:1400)	0.596
Platelet (10^9/L)	261019±77312	251 (97) (min:132-max:456)	242 (87) (min:116-max:717)	0.546
MPV (fL)	8.84±1.21	8.6 (1.6) (min:6.1-max:13.3)	8.7 (0.65) (min:6.6-max:11.9)	0.357
Hemoglobin (g/dL)	13.9±4.08	13.4 (1.9) (min:8.1-max:17.4)	13.7 (2.1) (min:9.7-max:13.7)	0.489
RDW (%)	14±1.51	13.8 (1.6) (min:11.3-max:21.7)	13.5 (1.5) (min:11.9-max:17.3)	0.583

Normally distributed data are presented as the mean± standard deviation. Non-normally distributed data are represented as the median (inter-quartile range) DM: Diabetes mellitus, HT: Hypertension, CVD: Cardiovascular diseases CRP:C-reactive protein, WBC: White blood cell, RDW: Red cell distrubition width, MPV: Mean Platelet Volume, GFR: Glomerular filtration rate, MBP: Mean blood pressure, SK:Solitary Kidney

Table 2. Comparison of basic characteristics and laboratory data between groups with congenital and acquired solitary kidney

Parameters	Group with congenital SK(n:75)	Group with acquired SK(n:129)	P
Gender (Female) (%)	39.5	60.5	0.296
DM (%)	30	70	0.312
CVD (%)	11.5	88.5	0.004
HT (%)	34.3	65.7	0.354
Follow-up time (years)	6 (6) (min:0.5-max:21)	7 (5) (min:1-max:19)	0.273
Age (year)	55 (27) (min:20-max:80)	60 (19) (min:25-max:80)	0.008
MBP (mmHg)	93 (17) (min:70-max:116)	93 (18) (min:77-max:120)	0.180
Urea at first admission (mg/dL)	34 (23) (min:17-max:113)	35 (17) (min:18-max:129)	0.662
Creatinine at first admission (mg/dL)	1.1 (0.52) (min:0.6-max:2.45)	1.2 (0.55) (min:0.7-max:3.6)	0.123
Proteinuria at first admission (mg/day)	100 (240) (min:100-max:4220)	100 (255) (min:100-max:4940)	0.832
eGFR at first admission (ml/min/1.73 m²)	64.5 (43.5) (min:19-max:120)	57 (27.7) (min:12-max:86)	0.041
Urea at last admission (mg/dL)	38 (27) (min:17-max:144)	41 (25) (min:18-max:155)	0.120
Creatinine at last admission (mg/dL)	1.04 (0.56) (min:0.5-max:5.61)	1.22 (0.59) (min:0.6-max:9.5)	0.043
Proteinuria at last admission (mg/day)	100 (340) (min:100-max:5360)	100 (290) (min:100-6560)	0.998
eGFR at last admission (ml/min/1.73 m²)	69±29 (min:7-max:127)	58±32.5 (min:3-max:118)	0.01
Annual change of eGFR (ml/min/1.73 m²)	0.78 (0.90) (min:-44.2;max:43.6)	0.77 (0.80) (min:-33.8. max:37.82)	0.321
Glucose (mg/dL)	97 (20) (min:80-max:250)	109 (23) (min:72-max:240)	0.387
Total Cholesterol (TC)(mg/dL)	189 (68) (min:95 max:409)	190 (59.5) (min:114-max:407)	0.551
HDL-cholesterol (mg/dL)	45 (17) (min:22-max:77)	43 (15) (min:19-max:89)	0.357
LDL-cholesterol (mg/dL)	112±32 (min:53-max:185)	113±35 (min:34-max:224)	0.957
Triglyceride (TG) (mg/dL)	134 (101) (min:45-max:537)	154 (127) (min:49-max:640)	0.066
TC/HDL-cholesterol ratio	4.13 (1.72) (min:2.2-max:9.74)	4.32 (1.95) (min:2.18-max:14)	0.193
LDL/HDL-cholesterol ratio	2.52±0.84 (min:0.9-max:4.96)	2.62±0.93 (min:0.3-max:5.96)	0.427
TG/HDL-cholesterol ratio	3 (3) (min:0.73-max:12.79)	3.3 (2.9) (min:0.79-max:22.37)	0.097
TG/non-HDL-cholesterol ratio	0.47±0.29 (min:0.14-max:1.11)	0.56±0.27 (min:0.1-max:1.35)	0.042
non-HDL-cholesterol (mg/dL)	141 (60) (min:65-max:367)	144 (52) (min:72-max:378)	0.389
Uric acid(mg/dL)	5.9±1.8 (min:2.6-max:11.4)	6.1±1.5 (min:2.6-max:9.5)	0.404
Albumin(g/dL)	4.3 (0.5) (min:3.2-max:5.3)	4.3 (0.5) (min:3.1-max:5.4)	0.835
CRP(mg/L)	1 (1.8) (min:0.28-max:2.2)	1 (1.5) (min:0.21-max:1.9)	0.819
WBC(10^6/L)	7700 (3300) (min:3500-max:12640)	7200 (2785) (min:4100-max:13300)	0.450
Neutrophil(10^6/L)	4600 (2100) (min:1900-max:9510)	4400 (2300) (min:2050-max:11400)	0.963
Lymphocyte(10^6/L)	2200 (1010) (min:800-max:4310)	200 (900) (min:800-max:4400)	0.131
Monocyte(10^6/L)	500 (300) (min:200-max:1400)	500 (200) (min:100-max:1100)	0.226
Platelet(10^9/L)	247 (193) (min:116-max:456)	250 (99) (min:132-max:717)	0.903
MPV(fL)	8.7 (1.3) (min:6.6-max:13.3)	8.6 (1.8) (min:6.1-max:11.9)	0.571
Hemoglobin(g/dL)	13.5 (1.8) (min:9.7-max:17)	13.6 (2.1) (min:8.1-max:13.2)	0.543
RDW(%)	13.9 (2) (min:11.3-max:18.3)	13.6 (1.5) (min:11.8-max:21.7)	0.438

Normally distributed data are presented as the mean± standard deviation. Non-normally distributed data are represented as the median (inter-quartile range) DM: Diabetes mellitus, HT: Hypertension, CVD: Cardiovascular diseases CRP:C-reactive protein, WBC: White blood cell, RDW: Red cell distrubition width, MPV: Mean Platelet Volume, GFR: Glomerular filtration rate, MBP: Mean blood pressure, SK: Solitary kidney

Table 3. Univariate and multivariate cox regression analysis for annual decline of eGFR (n:204)

Parameters	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	HR	95%CI	P	HR	95%CI	P
Age	1.005	0.991-1.020	0.449			
DM	1.088	0.744-1.592	0.663			
CVD	1.055	0.659-1.691	0.823			
MBP	1.003	0.985-1.021	0.750			
Glucose	1	0.995-1.005	0.936			
CRP	0.919	0.839-1.008	0.043	0.902	0.819-0.993	0.036
Albumin	0.854	0.533-1.368	0.511			
TC	1	0.996-1.004	0.997			
LDL-cholesterol	0.999	0.994-1.003	0.050	0.985	0.973-0.997	0.014
Non-HDL- cholesterol	1	0.996-1.004	0.062	1..013	1.002-1.023	0.016
TG/non-HDL- cholesterol	0.727	0.392-1.350	0.313	0.391	0.165-0.926	0.033
Causes of SK	0.933	0.641-1.360	0.720			

DM: Diabetes mellitus, CVD: Cardiovascular diseases CRP:C-reactive protein, GFR: Glomerular filtration rate, MBP: Mean blood pressure, TC: Total Cholesterol, TG: Triglyceride SK: Solitary Kidney

Table 4. Correlation analysis between CRP levels and cholesterol parameters (n:204)

Parameters	r	P
TC	0.154	0.027
TC/HDL- cholesterol	0.168	0.016
TG/HDL- cholesterol	0.136	0.049
Non-HDL- cholesterol	0.175	0.012

CRP:C-reactive protein, MBP: Mean blood pressure, TC: Total Cholesterol, TG Triglyceride

DISCUSSION

Solitary kidney disease is either congenital (renal agenesis) or acquired. GFR is preserved through initial adaptation mechanisms and glomerular hyperfiltration. However, extreme loads (e.g., hypertension, dyslipidemia) on the kidney increase intra-glomerular pressure, which can lead to permanent renal damage. Hypertension is the best known of these extreme loads. Increased intra-glomerular pressure in patients with chronic uncontrolled hypertension can cause podocyte damage and impaired perm-selectivity of the cleft diaphragm, which can lead to proteinuria (9). Despite of similar levels of proteinuria at first control, proteinuria level at last control and MBP were higher in group-I and they were negatively correlated with eGFR. However in regression analysis the effects of MBP and proteinuria on CKD progression were not found.

Dyslipidemia is another extreme load experienced by the kidney. The relationship between CKD and dyslipidemia is often defined by atherosclerosis in the microcirculation. However dyslipidemia also plays a role in the development of CKD by directly causing inflammation. Damage of dyslipidemia, especially FFA, on the kidney occurs through two mechanisms. First mechanism: Tubule cells need energy for reabsorption. Maximum ATP production occurs during the breakdown of FFA in mitochondria. If this breakdown is more than enough, reactive oxygen radical production increases. This leads to renal damage (10). Second mechanism: Excessive accumulation of FFA in tubule cells causes structural changes which eventually trigger apoptosis. The SLC27A2 gene is responsible for this mechanism (11). The reason for the excessive accumulation of FFA in tubule cells are decreased HDL levels and diminished cholesterol efflux capacity (12). In current study total cholesterol, LDL-cholesterol non-HDL-cholesterol, triglyceride/non-HDL-cholesterol ratio were higher in group-I. In regression analysis CRP, LDL-cholesterol, non-HDL-cholesterol, TG/non-HDL-cholesterol ratio are independent risk factors on annual decline of eGFR. There was also a correlation between CRP and total cholesterol, total cholesterol/HDL-cholesterol, triglyceride/non-HDL-cholesterol, triglyceride/HDL-cholesterol ratios, and non-HDL-cholesterol. It was understood that cholesterol levels affect renal function through the inflammation. Similar to current study, clinical studies have reported a relationship between renal dysfunction and dyslipidemia (13,14). In a study conducted with 48054 participants, total cholesterol, triglyceride, non-HDL-cholesterol, triglyceride/HDL-cholesterol ratio, LDL-cholesterol /HDL-cholesterol ratio was higher in CKD group compared to control group. In regression analysis triglyceride/HDL-cholesterol ratio and non-HDL-cholesterol /HDL-cholesterol ratio are independent risk factors of CKD progression (OR:1.121; OR:1.14 respectively) (15). In a meta-analysis, high intensity statins were found to improve decline in eGFR in population with CKD not requiring dialysis compared control (16).

In the current study, both in the regression analysis and in the comparison of groups, it was found that having an acquired or congenital solitary kidney did not affect the annual change of eGFR. Whereas, eGFR was lower in the acquired solitary kidney group both in the first and last admission. The reason for this low level may be due to the fact that the patients are a little older and comorbidities such as cardiovascular diseases are more common. In addition, the factor causing nephrectomy in individuals with acquired solitary kidney may have indirectly affected the other healthy kidney. Studies have shown that the risk of developing CKD is slightly higher in patients with acquired solitary kidney (8,17). Jaoude et al. (17) reported an inverse relationship between GFR and follow-up time in patients with acquired solitary kidney but not in those with congenital solitary kidney. They suggested that the adaptive response following renal mass reduction may begin much earlier in the case of congenital solitary kidney than in that of acquired solitary kidney. Furthermore because mature glomeruli have low mitotic activity, acquired solitary kidney can have a worse functional adaption.

The present study had some limitations. It was a retrospective study and the patients' medical treatments, body mass indexes and habits such as smoking and alcohol could not be evaluated completely. A single measurement of cholesterol levels and CRP may not provide sufficient accuracy for predicting the renal outcome.

CONCLUSION

Individuals with solitary kidneys have a higher risk of developing CKD. Inflammation and dyslipidemia must be paid attention to protect GFR. Besides the atherosclerosis in the microcirculation, dyslipidemia affect GFR through inflammation. Having a congenital or acquired single kidney has no effect on the annual decline of eGFR

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Research Ethics Committee of Ankara Training and Research Hospital (Date: 21.04.2020, Decision No: E-20/201).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Takemoto Y, Toshihide N. Economic issues of chronic kidney disease and End-Stage Renal Disease. Contrib Nephrol 2019; 198: 87-93.
2. Subbiah AK, Chhabra YK, Mahajan S. Cardiovascular disease in patients with chronic kidney disease: A neglected subgroup. Heart Asia 2016; 8: 56-61.
3. Sharabas I, Siddiqi N. Cardiovascular disease risk profiles comparison among dialysis patients. Saudi J. Kidney Dis. Transplant 2016; 27: 692-700.
4. Maggiore U, Budde K, Heemann U, et al. Long-term risks of kidney living donation: review and position paper by the ERA-EDTA DESCARTES working group. Nephrol Dial Transplant 2017; 32: 216–23.
5. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. New Engl J Med 2009; 360: 459–69.
6. Muzaale AD, Massie AB, Wang MC, et al. Risk of end-stage renal disease following live kidney donation. JAMA 2014; 311: 579–86.
7. Mjoen G, Hallan S, Hartmann A, et al. Long-term risks for kidney donors. Kidney Int 2014; 86: 162–7.
8. Kim S, Chang Y, Lee YR, et al. Solitary kidney and risk of chronic kidney disease. Eur J Epidemiol 2019; 34: 879-88.
9. Tantisattamo E, Dafoe DC, Reddy UG, et al. Current management of patients with acquired solitary kidney. Kidney Int Rep 2019; 4: 1205-18.
10. Nishi H, Higashihara T, Inagi R. Lipotoxicity in kidney, heart, and skeletal muscle dysfunction. Nutrients 2019; 11: 1664.
11. Khan S, Cabral PD, Schilling WP, et al. Kidney proximal tubule lipoapoptosis is regulated by fatty acid transporter-2 (FATP2). J Am Soc Nephrol 2018; 29: 81–91.
12. Rysz J, Gluba-Brzózka A, Rysz-Górzyńska M, Franczyk B. The role and function of HDL in patients with chronic kidney disease and the risk of cardiovascular disease. Int J Mol Sci 2020; 21: 601.
13. Chen SC1, Hung CC, Kuo MC, et al. Association of dyslipidemia with renal outcomes in chronic kidney disease. PLoS One 2013; 8: e55643.
14. Schaeffner ES, Kurth T, Curhan GC et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol 2003; 14: 2084–91.
15. Wen J , Chen Y, Huang Y. Association of the TG/HDL-C and non-HDL-C/HDL-C ratios with chronic kidney disease in an adult Chinese population. Kidney Blood Press Res 2017; 42: 1141-54.
16. Sanguankeo A, Upala S, Cheungpasitporn W, Ungpraser P, Knight EL. Effects of statins on renal outcome in chronic kidney disease patients: a systematic review and meta-analysis. PLoS One 2015; 10: e0132970.
17. Abou Jaoude P, Dubourg L, Bacchetta J, et al. Congenital versus acquired solitary kidney: is the difference relevant? Nephrol Dial Transplant 2011; 26: 2188–94.

Original Article

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The efficiency of Coban bandage on acute phase edema among patients undergoing a flexor tendon repair

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ABSTRACT

Introduction: To evaluate the efficiency of 3M Coban self-adherent wrap application on early (1-4 weeks) edema among patients undergoing surgery following a flexor tendon injury in Zone V or distal.

Material and Method: The study included 56 patients who had flexor tendon injuries. The patients were randomized into two groups by the computerized randomization method. Both groups were applied the "Modified Duran Protocol" (MDP) early passive mobilization exercises and "Retrograde Edema Massage". In addition, was applied 3M Coban self-adherent wrap to Group II. Finger circumferences was measured using a tape measure, and the pain intensity was evaluated with a visual analog scale (VAS). A goniometer was used to measure the joint range of motion (ROM), the Duruoz hand index (DHI) to evaluate functionality level, and the quality of life was investigated using the short form-36 (SF-36).

Results: The results showed that was statistically significant differences in both groups compared to pre-treatment ($p<0.05$). Edema, ROM, and all parameters of the DHI were found in both groups improved significantly ($p<0.05$). VAS pain scores at rest and activity were found significantly decreased in both groups compared to pre-treatment ($p<0.001$). In addition, pain at activity was found more significantly decreased in Group II (using bandage group). When it comes to the quality of life, there was a significant improvement in the SF-36 scores in both groups ($p<0.05$). In addition, increases in the scores on the "Physical Functioning" and "Physical Role" subscales were more significant in Group II ($p<0.05$).

Conclusion: In flexor tendon injuries, early rehabilitation and close follow-ups are likely to improve edema, upper extremity functions, and quality of life among patients. "Early Passive Mobilization Exercises (the Modified Duran Protocol)" and "Retrograde Edema Massage" are rather effective in edema treatment. Overall, we suggest that 3M Coban self-adherent wrap application also contributes to reducing pain at activity and improving physical functions following flexor tendon repairs.

Keywords: Flexor tendon injury, edema, 3M Coban self-adherent wrap

INTRODUCTION

When not treated early and correctly, flexor tendon injuries - prevalent among males of working age - may significantly restrict one's activities of daily living and cause lifelong problems (1,2). Surgeons may adopt different techniques in flexor tendon repairs. Yet, the shared purpose is to minimize the gap between tendon ends in the repair region, accelerate recovery, and increase tendon gliding and excursion (3). In the literature, surgical techniques applying 4 knots with 4-0 and 5-0 prolene suture materials and the Kessler technique are encouraged, as well as epitendinous repair (4). The easy-to-apply and practical nature (consuming less time) is the distinctive feature of the modified Kessler + epitendinous suture technique (5).

Many rehabilitation methods come to mind in flexor tendon injuries. Postoperative active or passive motion programs are often cited to improve postoperative outcomes for repaired tendons (6,7). The Modified Duran Protocol is among these programs. This protocol suggests that 3-5 mm of passive motion of the tendon anastomosis would effectively prevent tendon adhesions (8). The passive, controlled motions may protect the newly repaired tendon and help control the tension in the repaired area (9). For this purpose, a dorsal splint is used by limiting the wrist to 20° and MCP joints to 40-50° of flexion and keeping fingers extended. A splint allows passive flexion of the fingers but hinders the extension beyond its boundaries (10). Unlike the Duran and Houser protocol, a splint is not

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supplemented with a tape, and the interphalangeal joints are kept extended between exercises or overnight. Patients individually perform passive flexion-extension exercises.

Edema may occur in hands secondary to injury and surgery in the early period or due to venous return insufficiency caused by decreased motion after local trauma. It is quite common in flexor tendon injuries and adversely affects the rehabilitation process (11). Extremity elevation, exercises, retrograde massage, and elastic compressions are used to treat edema (12). As a kind of compression method, Coban bandages will be effective in dealing with edema and improving hand functionality when used in the early period, especially in patients with flexor tendon injuries with excessive soft tissue edema.

The relevant literature shows not much interest in hand edema and Coban bandage after flexor tendon injuries. In our literature review, we could unfortunately not encounter any study evaluating the efficiency of this bandage in the rehabilitation program applied following flexor tendon repairs. Therefore, we aimed to investigate the effectiveness of 3M Coban self-adherent wrap involved in the early period (1-4 weeks) on edematous hands and fingers repaired with the modified Kessler surgical technique after flexor tendon injuries in zone V or its distal.

MATERIAL AND METHOD

The Ethics Committee of Kırıkkale University granted ethical approval to our study (Date: 11/03/2021, Decision No: 2021/05-2021.03.02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was carried out with the permission of Ankara City Hospital Department of Physical Therapy and Rehabilitation Traumatic Hand Rehabilitation Clinic.

This study included 56 patients (40 males and 16 females) aged 18 years and over who applied to the traumatic hand outpatient clinic between April 2021 and September 2021, underwent a zone V or distal flexor tendon surgery with the modified Kessler suture technique, who were in the acute period (1-4 weeks) with edema on the volar or dorsal surface of the finger-hand. All patients were informed about the study the study and signed the informed consent form. Those with infection, malignancy, circulatory problems, steroid-nonsteroid medication, cognitive dysfunction, and open wounds were excluded from the study.

After recording their demographic characteristics, the patients were randomized into two groups by the computerized randomization method. Group I included 19 males (mean age: 30.05±10.45 years) and 9 females (mean age: 31.22±15.10 years), while Group II was composed of 21 males (mean age: 36.85±12.31 years) and 7 females (mean age: 28.85±8.49 years).

During the postoperative rehabilitation phase, both groups were applied the "Modified Duran Protocol" (MDP) early passive mobilization exercises(13) and "Retrograde Edema Massage". In addition, was applied 3M Coban Self-Adherent Wrap to Group II for their edematous fingers-hands. All patients were provided the treatment for 4 weeks and was called them for control examinations in the 1st, 2nd, and 4th weeks.

According to the Modified Duran Protocol, a dorsal blocking splint was used in all patients for 4 weeks in all patients for 4 weeks, keeping the wrist at 20° flexion, MCP joints 40-50° flexion, and fingers extended. Interphalangeal (IF) joints were taped in extension between exercises and at night (14). The patients were advised to perform early passive mobilization exercises as passive flexion and extension for the distal interphalangeal (DIP), proximal interphalangeal (PIF), and metacarpophalangeal (MCP) joints ten times every hour and hold them for five seconds in each position (14). In addition, the patients were explained how to do retrograde edema massage for edema control: retrograde edema massage refers to effleurage motions with slight pressure from the fingertip to the palm (from distal to proximal) in the plaster cast (15,16). The patients were warned to perform exercises and massage without removing the splint. Rehabilitation practices were taught to each patient by the same physiotherapist, and were asked to do them every hour during the day.

It is well-known that edema caused by surgery or trauma severely limits movements, slows down recovery, and prolongs the return to daily life. Therefore, edema treatment should be included in a rehabilitation program (17). In addition to the rehabilitation program, 3M Self-Adherent Wrap, which is considered helpful in postoperative edema, was applied to the patients in Group II. Each bandage was wrapped circularly (on its own stretch) from distal to proximal, covering the wrist, edematous finger, and the volar and dorsal parts of the hand (**Figure**). The patients were advised to use it between exercises and remove it at night and during exercises (12).

Environmental and volumetric measurements are utilized to determine edema severity (19). Peripheral measurement refers to measuring the circumference of the IF and MCF joints with a tape measure, which is a valid, reliable, widely adopted method (20). This method is usually helpful if there is edema in one or both fingers since a small amount of edema cannot be identified with a

volumetric measurement. In a volumetric measurement, one's hand and wrist are placed vertically in a volüme meter, and the volume of fluid overflowed by the hand is calculated. In this study was preferred the tape measure method due to the pandemic. The patients' hand and wrist circumferences were measured using a tape measure in a way of completely surrounding joints and not squeezing soft tissues (21). DIP, PIP, MCP, and wrist circumferences were evaluated at different stages of the treatment (pre-treatment (PT), 1st week (T1), 2nd week (T2), and 4th week (T4) control examinations) and results were compared.

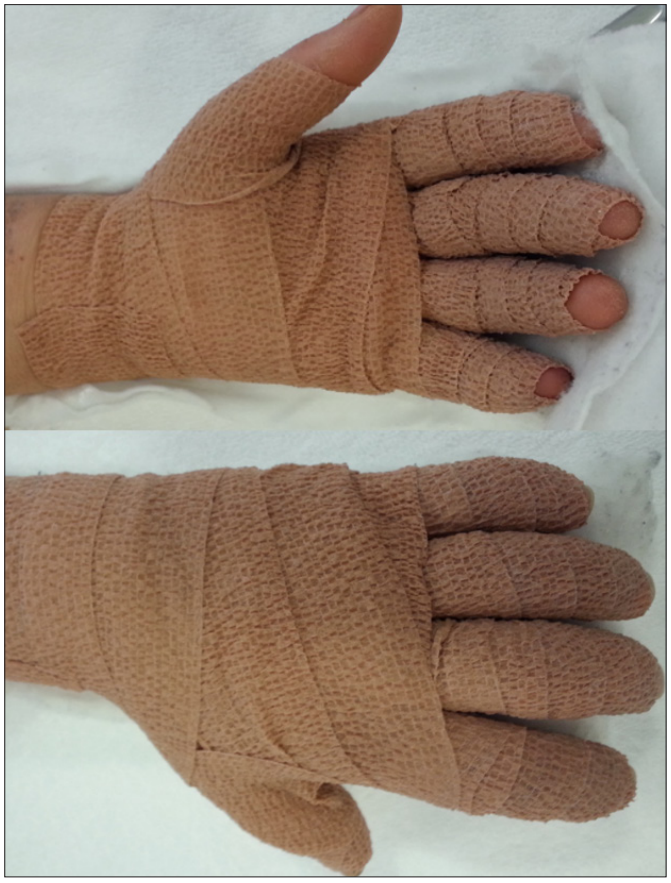

Figure. Coban self-adhesive bandage (3M) application

Range of Motion (ROM) of all joints of the injured hand was measured passively with a goniometer at PT, T1, T2, and T4 control examinations. ROM is one of the most commonly used outcome variables after hand tendon injuries and can be measured on the dorsum or lateral of the hand (22).

The patients' functionality levels were determined using the Duruoz Hand Index (DHI) at PT and T4 examination. The index consists of 18 items on the ability to do some basic hand movements in Daily life activities and is scored on a scale ranging between 0 (no difficulty) and 5 (impossible to do); a higher score refers to greater activity restriction and difficulty (23).

The pain severity at rest and activity was assessed using a Visual Analog Scale (VAS) at PT and T4 examination. For the VAS assessments, the patients were told about the meanings of the numbers 0 (no pain)-10 (severe pain) placed on a 10 cm line, and we asked them to mark their pain severity on this 10 cm line. Pain severity was identified considering the distance between the marked number and the starting point (24).

Finally, quality of life among the patients was evaluated using the Short Form-36 (SF-36) at PT and T4 examination. It is a 36-item scale consisting of the social functioning, physical functioning, physical role, emotional role, bodily pain, vitality, general health, and mental health subscales. Each subscale is scored on a scale ranging from 0 (poorest quality of life) and 100 (greatest quality of life) (25).

Statistical Analysis

Statistical Analysis were carried out using the Statistical Package for the Social Sciences (SPSS, version 23.0; Inc, Chicago, IL, USA). The patients were assigned to the groups using the computerized randomization method to balance their prognostic factors. The normality of distribution was checked using the Shapiro-Wilks test. Continuous variables were presented as mean±standard deviation and median (minimum-maximum) and categorical variables as numbers and percentages. Groups were compared by Independent Sample t-test in terms of normally distributed numerical variables. In contrast, groups were compared by Mann-Whitney U test for numerical variables that were not normally distributed. Multiple comparisons of the repeated measured between groups were performed using parametric a mixed-design analysis of variance tests (mixed-design ANOVA) or non-parametric two-way Friedman's tests depending on the normality of distribution. All statistically analysis was performed at the 95% confidence interval and p-value <0.05 was accepted as statistically significant.

RESULTS

The study was carried out with 56 patients [40 males (71.4%), 16 females (28.6%)] with a mean age of 32.64±11.96 years. **Table 1** presents the demographic, injury, and pain characteristics of the participants.

The results revealed that edema in both groups improved significantly from PT to T1 examination, from T1 to T2 examination compared to the baseline parameters ($p<0.05$). Comparing the circumference measurements in the T2 and T4 examination, edema decreased significantly in Group I ($p<0.05$); however not significantly in Group II ($p>0.05$). The differences between the groups were not significant ($p>0.05$) (**Table 2**).

The degree of joint range of motion (passive) increased statistically in both groups compared to pre-treatment (p<0.001); nevertheless, the difference was not significant between the groups (p>0.05) (**Table 3**). Although there were significant differences within the groups by all parameters of the Duruoz Hand Index compared to pre-treatment, between-group differences were not significant (p>0.05). VAS pain scores at rest and activity showed significant decreases in both groups compared to pre-treatment (p<0.05). In addition, pain at activity was found more significantly decreased in Group II (using bandage group) (p<0.001), but improvement in pain at rest was similar between the groups (p>0.05). Within and between-group comparisons for functional status and pain severity are shown in **Table 4**.

Table 1. Patients' demographic, injury, and pain characteristics

Variables	All groups n=56	Group I n=28	Group II n=28	p value
Age, (year)				0.111
Mean±SD	32.64±11.96	30.42±11.86	34.85±11.86	
Med (min-max)	29.50 (18.00-61.00)	26.50 (18.00-55.00)	32.50 (18.00-61.00)	
Sex, n (%)				0.554
Male	40 (71.4)	19 (67.9)	21 (75)	
Female	16 (28.6)	9 (32.1)	7 (25)	
Educational attainment, n (%)				0.507
Primary school	14 (25)	6 (21.4)	8 (28.6)	
High school	32 (57.1)	18 (64.3)	14 (50)	
Undergraduate or above	10 (17.9)	4 (14.3)	6 (21.4)	
Smoking, n (%)				0.592
Yes	30 (53.6)	16 (57.1)	14 (50)	
No	26 (46.4)	12 (42.9)	14 (50)	
Occupation, n (%)				0.165
Worker	31 (55.4)	15 (53.6)	16 (57.1)	
Civil servant	4 (7.1)	2 (7.1)	2 (7.1)	
Retired	6 (10.7)	1 (3.6)	5 (17.9)	
Student	10 (17.9)	8 (28.6)	2 (7.1)	
Housewife	5 (8.9)	2 (7.1)	3 (10.7)	
Dominant hand, n (%)				0.388
Right	50 (89.3)	24 (85.7)	26 (92.9)	
Left	6 (10.7)	4 (14.3)	2 (7.1)	
Injured hand, n (%)				0.422
Dominant	29 (51.8)	16 (57.1)	13 (46.4)	
Non-dominant	27 (48.2)	12 (42.9)	15 (53.6)	
Type of injury, n (%)				0.378
Knife	30 (53.6)	12 (42.9)	18 (64.3)	
Glass	18 (32.1)	11 (39.3)	7 (25)	
Spiral stone	4 (7.1)	3 (10.7)	1 (3.6)	
Metal	4 (7.1)	2 (7.1)	2 (7.1)	
Number of injured fingers, n (%)				0.073
1 finger	36 (64.3)	14 (50)	22 (78.6)	
2 fingers	15 (26.8)	10 (35.7)	5 (17.9)	
3 fingers and more	5 (8.9)	4 (14.3)	1 (3.6)	
Treatment initiation, n (%)				0.607
1. week	12 (21.4)	6 (21.4)	6 (21.4)	
2. week	29 (51.8)	16 (57.1)	13 (46.4)	
3. week	13 (23.2)	5 (17.9)	8 (28.6)	
4. week	2 (3.6)	1 (3.6)	1 (3.6)	
Comorbidity, n (%)				0.716
No	47 (83.9)	24 (85.7)	23 (82.1)	
Yes	9 (16.1)	4 (14.3)	5 (17.9)	
VAS at rest, (cm)				0.398
Mean±SD	3.50±2.19	3.75±2.22	3.25±2.17	
Med (min-max)	3.00 (1.00-9.00)	3.50 (1.00-8.00)	3.00 (1.00-9.00)	
VAS on movement, (cm)				0.144
Mean±SD	3.73±1.91	3.35±1.78	4.10±1.98	
Med (min-max)	3.00 (1.00-8.00)	3.00 (1.00-7.00)	3.00 (1.00-8.00)	

* p<0.05. SD: Standard deviation. Min: Minimum. Max: Maximum. VAS: Visual Analog Scale. cm: centimeter

Table 2. Within and between-group comparisons for edema reduction between the patients with a flexor tendon injuries

Variables	Group I n=28 Mean±SD (centimeter)	p	Group II n=28 Mean±SD (centimeter)	p	p value
1DIP					
PT-T1	6.92±0.65-6.76±0.64	<0.001*	7.10±0.60-6.91±0.59	<0.001*	0.553
T1-T2	6.76±0.64-6.58±0.64	<0.001*	6.91±0.59-6.76±0.51	0.003*	0.602
T2-T4	6.58±0.64-6.47±0.61	0.007*	6.76±0.51-6.66±0.55	0.002*	0.943
PT-T4	6.92±0.65-6.47±0.61	<0.001*	7.10±0.60-6.66±0.55	<0.001*	0.957
2DIP					
PT-T1	5.66±0.43-5.48±0.44	<0.001*	5.85±0.72-5.62±0.57	<0.001*	0.562
T1-T2	5.48±0.44-5.36±0.45	<0.001*	5.62±0.57-5.42±0.55	<0.001*	0.071
T2-T4	5.36±0.45-5.24±0.40	0.019*	5.42±0.55-5.37±0.55	0.143	0.244
PT-T4	5.66±0.43-5.24±0.40	<0.001*	5.85±0.72-5.37±0.55	<0.001*	0.578
3DIP					
PT-T1	5.62±0.48-5.50±0.47	0.007*	5.99±0.64-5.74±0.50	<0.001*	0.084
T1-T2	5.50±0.47-5.32±0.49	<0.001*	5.74±0.50-5.59±0.54	<0.001*	0.587
T2-T4	5.32±0.49-5.22±0.49	0.015*	5.59±0.54-5.50±0.59	0.038*	0.804
PT-T4	5.62±0.48-5.22±0.49	<0.001*	5.99±0.64-5.50±0.59	<0.001*	0.294
4DIP					
PT-T1	5.37±0.51-5.22±0.49	<0.001*	5.60±0.54-5.36±0.49	<0.001*	0.145
T1-T2	5.22±0.49-5.08±0.48	0.001*	5.36±0.49-5.25±0.50	0.002*	0.605
T2-T4	5.08±0.48-4.97±0.48	0.011*	5.25±0.50-5.13±0.50	<0.001*	1.000
PT-T4	5.37±0.51-4.97±0.48	<0.001*	5.60±0.54-5.13±0.50	<0.001*	0.439
5DIP					
PT-T1	5.01±0.48-4.78±0.46	<0.001*	5.32±0.56-5.06±0.52	<0.001*	0.664
T1-T2	4.78±0.46-4.68±0.41	0.004*	5.06±0.52-4.94±0.53	0.001*	0.633
T2-T4	4.68±0.41-4.59±0.45	0.026*	4.94±0.53-4.87±0.52	0.092	0.695
PT-T4	5.01±0.48-4.59±0.45	<0.001*	5.32±0.56-4.87±0.52	<0.001*	0.676
2PIP					
PT-T1	6.82±0.51-6.63±0.57	<0.001*	7.07±0.70-6.81±0.56	<0.001*	0.310
T1-T2	6.63±0.57-6.55±0.60	0.001*	6.81±0.56-6.65±0.58	0.001*	0.218
T2-T4	6.55±0.60-6.43±0.57	0.016*	6.65±0.58-6.58±0.54	0.227	0.443
PT-T4	6.82±0.51-6.43±0.57	<0.001*	7.07±0.70-6.58±0.54	<0.001*	0.262
3PIP					
PT-T1	6.88±0.63-6.70±0.59	0.003*	7.19±0.64-6.94±0.54	0.001*	0.459
T1-T2	6.70±0.59-6.57±0.62	0.001*	6.94±0.54-6.78±0.55	0.001*	0.552
T2-T4	6.57±0.62-6.44±0.59	0.001*	6.78±0.55-6.75±0.60	0.417	0.081
PT-T4	6.88±0.63-6.44±0.59	<0.001*	7.19±0.64-6.75±0.60	<0.001*	0.908
4PIP					
PT-T1	6.68±0.72-6.45±0.66	<0.001*	6.83±0.70-6.48±0.57	<0.001*	0.093
T1-T2	6.45±0.66-6.31±0.63	0.001*	6.48±0.57-6.32±0.61	0.005*	0.775
T2-T4	6.31±0.63-6.17±0.68	0.003*	6.32±0.61-6.29±0.57	0.062	0.147
PT-T4	6.68±0.72-6.17±0.68	<0.001*	6.83±0.70-6.29±0.57	<0.001*	0.790
5PIP					
PT-T1	5.92±0.63-5.69±0.60	<0.001*	6.28±0.71-6.03±0.71	<0.001*	0.765
T1-T2	5.69±0.60-5.55±0.55	0.002*	6.03±0.71-5.85±0.64	<0.001*	0.488
T2-T4	5.55±0.55-5.45±0.58	0.003*	5.85±0.64-5.80±0.64	0.240	0.289
PT-T4	5.92±0.63-5.45±0.58	<0.001*	6.28±0.71-5.80±0.64	<0.001*	0.964
MCP					
PT-T1	20.65±1.56-20.33±1.70	<0.001*	21.30±1.65-20.88±1.64	<0.001*	0.408
T1-T2	20.33±1.70-20.11±1.68	0.020*	20.88±1.64-20.62±1.67	<0.001*	0.704
T2-T4	20.11±1.68-19.90±1.69	0.004*	20.62±1.67-20.57±1.78	0.444	0.124
PT-T4	20.65±1.56-19.90±1.69	<0.001*	21.30±1.65-20.57±1.78	<0.001*	0.898
WRIST					
PT-T1	17.63±1.35-17.49±1.35	0.020*	17.72±1.32-17.47±1.35	0.001*	0.241
T1-T2	17.49±1.35-17.35±1.31	0.002*	17.47±1.35-17.29±1.34	0.002*	0.555
T2-T4	17.35±1.31-17.17±1.36	0.010*	17.29±1.34-17.30±1.47	0.918	0.051
PT-T4	17.63±1.35-17.17±1.36	<0.001*	17.72±1.32-17.30±1.47	<0.001*	0.699

* p<0.05. SD: Standard deviation. PT: Pre-treatment. T1: first-week treatment. T2: second-week treatment. T4: fourth-week treatment DIP: Distal interphalangeal joint. PIP: Proximal interphalangeal joint MCP: metacarpophalangeal joint

When it comes to quality of life, there were significant differences in Group I all scores except "Physical Role" and "Emotional Role" subscales, and in Group II all scores except "Emotional Role" subscale compared to pre-treatment in the SF-36 scores (p<0.05). In addition, increases in the scores on the "Physical Functioning" and "Physical Role" subscales were more significant in Group II (using bandage group) than in Group I (p<0.05). No statistically significant difference was found between groups other subscales (p>0.05) (**Table 5**).

DISCUSSION

The present study explored the efficiency of 3M Coban Self-Adherent Wrap application on edema and rehabilitation in flexor tendon injuries. The study was found Coban bandage application, along with other conventional treatments, to be significantly helpful in reducing pain at the activity. In addition, the improvements in some parameters of quality of life (e.g, physical function and physical role) were significantly greater in those using Coban bandages.

Table 3. Within and between-group comparisons for joint range of motion (passive) values between the patients with flexor tendon injuries

Variables		Group I n=28		Group II n=28		p value
		Mean±SD (degree)	p	Mean±SD (degree)	p	
1DIP	PT-T4	50.53±13.07-75.35±9.80	<0.001*	54.82±13.15-77.50±10.22	<0.001*	0.505
2DIP	PT-T4	40.17±11.09-64.28±8.68	<0.001*	42.67±12.72-65.17±8.10	<0.001*	0.573
3DIP	PT-T4	42.32±8.86-65.00±8.81	<0.001*	44.28±11.84-64.28±9.30	<0.001*	0.341
4DIP	PT-T4	42.32±12.20-66.07±10.57	<0.001*	44.82±10.58-65.17±10.13	<0.001*	0.302
5DIP	PT-T4	44.46±10.99-66.42±10.61	<0.001*	40.89±10.27-63.39±10.97	<0.001*	0.877
2PIP	PT-T4	68.75±14.82-95.00-10.18	<0.001*	70.35±19.90-96.78±9.54	<0.001*	0.963
3PIP	PT-T4	70.00±13.47-95.53±9.46	<0.001*	71.25±16.30-94.64±10.17	<0.001*	0.519
4PIP	PT-T4	70.35±18.50-94.10±10.54	<0.001*	75.17±15.66-96.42±9.70	<0.001*	0.517
5PIP	PT-T4	71.78±14.09-95.35±10.26	<0.001*	67.50±15.42-93.03±12.49	<0.001*	0.616
MCPfl	PT-T4	40.53±12.93-71.42±11.61	<0.001*	46.25±11.51-70.53±11.08	<0.001*	0.138
WRISTfl	PT-T4	37.85±16.01-70.17±15.30	<0.001*	43.21±13.20-70.53±9.65	<0.001*	0.171
WRISTex	PT-T4	11.78±15.22-42.67±20.65	<0.001*	20.17±13.43-53.92±14.74	<0.001*	0.541

* p<0.05. SD: Standard deviation. PT: Pre-treatment. T4: fourth-week treatment DIP: Distal interphalangeal joint. PIP: Proximal interphalangeal joint MCP: metacarpophalangeal joint. Fl: Flexion. Ex: Extension

Table 4. Within and between-group comparisons for functional status and pain scores between the patients with flexor tendon injuries

Variables		Group I n=28		Group II n=28		p value
		Mean±SD	p	Mean±SD	p	
DHI kitchen	PT-T4	40.00±0.00-13.78±5.06	<0.001*	39.32±2.49-11.75±4.39	<0.001*	0.282
DHI dressing	PT-T4	10.00±0.00-2.71±1.24	<0.001*	9.57±1.59-2.50±0.88	<0.001*	0.569
DHI hygiene	PT-T4	10.00±0.00-2.50±1.20	<0.001*	9.53±1.75-2.32±1.05	<0.001*	0.515
DHI at the office	PT-T4	10.00±0.00-3.14±1.38	<0.001*	9.92±0.37-2.53±1.10	<0.001*	0.118
DHI other	PT-T4	20.00±0.00-5.42±2.21	<0.001*	19.53±1.71-4.75±1.99	<0.001*	0.716
DHI tota	PT-T4	90.00±0.00-27.57±9.10	<0.001*	87.89±7.74-23.85±7.88	<0.001*	0.510
VAS at rest (cm)	PT-T4	3.75±2.22-0.96±0.92	<0.001*	3.25±2.17-0.60±0.91	<0.001*	0.735
VAS on movement (cm)	PT-T4	3.35±1.78-1.46±1.26	0.004	4.10±1.98-0.92±1.01	<0.001*	<0.001*

* p<0.05. SD: Standard deviation. PT: Pre-treatment. T4: fourth-week treatment. DHI: Duruoz Hand Index. VAS: Visual Analog Scale. Cm: Centimeter

Table 5. Within and between-group comparisons for sf-36 scores between the patients with flexor tendon injuries

Variables		Group I n=28		Group II n=28		p value
		Mean±SD	p	Mean±SD	p	
SF36 Physical functioning	PT-T4	61.96±4.15-81.42±4.48	<0.001*	60.17±0.94-83.03±4.37	<0.001*	0.002*
SF36 Role physical	PT-T4	33.92±23.77-34.82±22.91	0.326	25.00±24.53-30.35±20.81	0.011*	0.044*
SF36 Bodily pain	PT-T4	54.10±25.73-86.07±16.05	<0.001*	50.08±26.07-84.64±16.86	<0.001*	0.692
SF36 General health	PT-T4	76.78±13.62-83.39±10.71	0.001*	73.57±14.06-81.42±12.75	<0.001*	0.570
SF36 Vitality	PT-T4	38.39±24.57-61.96±20.69	<0.001*	40.71±23.04-68.39±22.40	<0.001*	0.545
SF36 Social functioning	PT-T4	55.35±19.37-76.33±14.16	<0.001*	57.58±21.33-76.78±18.85	<0.001*	0.716
SF36 Role emotional	PT-T4	27.37±24.10-28.56±23.51	0.326	32.13±23.10-35.71±25.56	0.083	0.307
SF36 Mental health	PT-T4	53.85±25.70-67.85±21.37	0.004*	44.85±24.13-70.00±22.82	<0.001*	0.075

* p<0.05. SD: Standard deviation. PT: Pre-treatment. T4: fourth-week treatment. SF-36: Short Form 36 Health Questionnaire

The mean age of 56 patients (40 male, 16 female) was 32.64±11.96 years. Fifty patients presented with a right-hand injury, 6 with a left-hand injury. Among them, 29 patients (51.8%) had a dominant hand injury. Seven (12.5%) patients had a zone I flexor tendon injury, 29 (51.8%) had a zone II injury, 9 (16.1%) had a zone III injury, 6 (10.7%) had a zone IV injury, and 5 (8.9%). In their study, Manninen et al. (2) examined the epidemiology of hand flexor tendon injuries in the northern Finnish population. The mean age of the sample (106 patients) was 39±16 years, and flexor tendon injuries were more common in males than females, especially among those of working age. More than half of the patients (n=59, 56%) had a right-hand injury, 47 (44%) had a left-hand injury. Thirty-five (33%) patients had a zone I flexor tendon injury, 59 (56%) had a zone II injury, 1 (0.9%) had a zone III injury, 3 (2.8%) had a zone IV injury, and 7 (6.6%) had a zone V injury. The reported rates were similar to those in our study.

The available data on the edema-reducing effect of 3M Coban Self-Adherent Wrap application are quite limited. Moreover, we could not encounter any study evaluating the efficiency of Coban bandage application within a rehabilitation program after flexor tendon repairs. Lowell et al. (21) investigated the efficiency of 3M Coban Self-Adherent Wrap application on burned hand edema and followed up a 59-year-old male patient for four weeks. The results revealed that the treated hand had less edema, greater range of motion (active), more increased grip strength, and more improved dexterity compared to the other hand. In their randomized controlled study, Moffatt et al. (26) evaluated 82 patients to compare the effects of shortstretch bandage and 3M Coban Self-Adherent Wrap application on upper-extremity volume (edema) and their use at different frequencies in lymphedema patients. The patients were divided into four groups and followed up for 19 days. Group I (22 patients) had a short-stretch bandage five times a week; Group II (22 patients), Group III (20 patients), and Group IV (18 patients) had a Coban bandage twice a week, three times a week, and five times a week, respectively. The results showed that 3M Coban Self-Adherent Wrap application decreased upperextremity volume (edema), which was greater in Group III than in the other groups.

In flexor tendon injuries, a limited motion protocol is adopted after surgery in most cases. Early tendon motion reduces adhesion, increases gliding, and promotes healing (27). In a study comparing early active and passive mobilization protocols, Frueh et al. (28) divided 159 fingers (132 patients) undergoing flexor tendon repairs into two groups and found no significant differences between the group with early passive mobilization protocol (138 fingers) and the group with early active mobilization protocol (21 fingers). In another study, Kitis et al. (29) recruited 192 patients (263 fingers) and divided those with a zone II flexor tendon injury into two groups. They applied the modified Kleinert protocol to one group (97 patients; 137 fingers) and controlled passive motion protocol to the other group (94 patients; 126 fingers). Using the Buck-Gramcko scale at the end of the 12th week, the researchers found that total active motion was 87% excellent in the modified Kleinert protocol group and 75% excellent in the controlled passive motion protocol group. In our study, early passive mobilization exercises were applied to both groups following the Modified Duran Protocol. At the end of the fourth week, the groups had significant improvements in the range of motion and functional use of the hand and finger joints compared to the baseline parameters.

Bircan et al. (30) applied the Modified Kleinert and Modified Duran Protocols to 18 patients with a zone V flexor tendon injury and evaluated rehabilitation outcomes using the Buck-Gramcko scale. The researchers reached excellent results in 92.8% of the fingers after the rehabilitation program, which lasted for an average of 20 months. Besides, Chan et al. (31) evaluated 16 patients (21 fingers) with a zone II flexor tendon injury repaired with the modified Kessler suture technique. After an average of 130-day rehabilitation program consisting of active extension against band resistance, band-aided passive flexion, and controlled passive flexion-extension exercises, the functional results were excellent and good in 81% of the fingers according to the Buck-Gramcko scale.

Strickland and Glogovac (32) divided 37 patients (50 fingers) undergoing flexor tendon repairs into two groups and applied immobilization to one group (25 fingers) and early passive motion (a slight modification of the Duran and Houser protocols) to the other group (25 fingers). They observed that joint motion was significantly better in the second group and reported early passive motion might be an effective technique after flexor tendon repairs in the postoperative period.

In a study, Turan et al. (33) attempted to validate the DHI in diabetic hand dysfunction and concluded it to be a reliable, practical scale to assess hand dysfunction in diabetic patients accurately. Moreover, Erçalık et al. (34) explored the reliability and validity of the DHI among 65 patients (140 fingers) undergoing flexor tendon repairs. They concluded the DHI to be a reliable and valid questionnaire to evaluate the dexterity restrictions and clinical course of patients with traumatic hand injuries. In this study, all DHI parameters improved significantly in both groups compared to PT, but the differences between the groups were similar.

It seems there is a lack of interest in the literature regarding the relationship between 3M Coban Self-Adherent Wrap application and the VAS pain at activity in traumatic hand injuries. In their randomized controlled study, Jonker et al. (35) explored the impacts of 3M Coban self-adherent wrap application on the pain profile after osteotomy and evaluated patients using a 10 cm descriptive pain scale at PT and during the fourth-week control examination. The results showed bandage application altered the pain profile among the patients, supporting our study. Lee et al. (36) scrutinized the mechanism and treatment of trigger finger secondary to neglected partial flexor tendon rupture. They performed debridement and repair of the ruptured tendon and discovered the postoperative VAS pain scores significantly decreased compared to PT. In this study, there were found the VAS pain at rest and activity significantly decreased in both groups compared to PT, while pain at actvity decreased more in Group II (bandage using group) at the fourth week compared to Group I. Such findings may imply that 3M Coban Self-Adherent Wrap application is an effective treatment method in reducing pain at activity in flexor tendon injuries.

On the other hand, Galasso et al. (37) assessed quality of life among patients with carpal tunnel syndrome and found a significant improvement in most of the SF-36 subscales (excluding general health, vitality, and mental health) when compared to baseline measurement. In a study by Oktayoğlu et al. (38) to evaluate hand functions in patients with idiopathic cervical dystonia, quality of life was assessed with SF-36. The results revealed significant differences between the groups by all SF-36 subscales. In this study, both groups significantly had increased scores on all SF- 36 subscales compared to the baseline measurements. Yet, improvements in "Physical Functioning" and "Physical Role" subscales were more significant in Group II (bandage using group) after treatment. Hence, 3M Coban self-adherent wrap application may contribute to the improvements in physical functions of patients with flexor tendon injuries.

CONCLUSION

In flexor tendon injuries, early rehabilitation and close follow-ups help improve edema, upper extremity functions, and quality of life among patients. "Modified Duran Protocol" early passive mobilization exercises and "Retrograde Edema Massage" are efficient in edema treatment. Besides, 3M Coban self-adherent wrap application offers an extra advantage in reducing pain at activity and improving physical functions in flexor tendon injuries.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Medical Faculty Non-interventional Clinical Researchs Ethics Committee (Date: 11/03/2021, Decision No: 2021/05-2021.03.02).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Kuran, B. Tendon yaralanmaları ve rehabilitasyonu. içinde: El Rehabilitasyonu. ed. Çerezci, Ö, Ataker Y, Canbulat N, Güdemez E. Amerikan Hastanesi Derg 2013; 171-99.
2. Manninen M, Karjalainen T, Määttä J, Flinkkilä T. Epidemiology of flexor tendon injuries of the hand in a Northern Finnish population. Scand J Surg 2017; 106: 278-82.
3. Dy CJ, Hernandez-Soria A, Ma Y, Roberts RT, Daluiski A. Complications after flexor tendon repair: a systematic review and meta-analysis. J Hand Surg 2012; 37: 543-51.
4. Gibson PD, Sobol GL, Ahmed IH. Zone II flexor tendon repairsin the United States: trends in current management. J Hand Surg 2017; 42: e99-e108.
5. Pişkin A, Yücetürk A, Tomak Y, et al. Tendon repair with the strengthened modified Kessler, modified Kessler, and Savage suture techniques: a biomechanical comparison. Acta Orthop Traumatol Turc 2007; 41: 238-43.
6. Kleinert H. Primary repair of lacerated flexor tendons in" no man's land". J Bone Joint Surg 1967; 49: 577.
7. Lee H. Double loop locking suture: A technique of tendon repair for early active mobilization Part I: Evolution of technique and experimental study. J Hand Surg 1990; 15: 945-52.
8. Çetin A, Dinçer F, Keçik A, Çetin M. Rehabiliation of flexor tendon injuries by use of a combined regimen of modified Kleinert and modified Duran techniques. Am J Physical Med Rehab 2001; 80: 721-8.
9. Duran RJ, Houser RG, Coleman CR, Stover MG. Management of flexor tendon lacerations in zone 2 using controlled passive motion postoperatively. Tendon Surg in the Hand. St Louis: CV Mosby, 1978: 178-82.

10. Gül Ş. Fleksör tendon kesisi olan hastalarda erken aktif mobilizasyon ve modifiye duran protokollerinin etkinliğinin retrospektif olarak incelenmesi, in Fiziksel Tıp ve Rehab A.B.D 2019, Hacettepe Üniversitesi: Ankara.
11. Uysal M. Deformite cerrahisi komplikasyonları ve tedavisi. Sakarya Üniversitesi Tıp Fakültesi, Ortopedi ve Travmatoloji Anabilim Dalı, Sakarya. TOTBİD 2020; 19: 312–9.
12. Leclère FM, Mathys L, Juon B, Vögelin E. The role of dynamic ultrasound in the immediate conservative treatment of volar plate injuries of the PIP joint: a series of 78 patients. Plastic Surg 2017; 25: 151-6.
13. Duran R. A preliminary report in the use of controlled passive motion following flexor tendon repair in zones II and III. J Hand Surg 1976; 1: 79.
14. Büyükturan Ö, Ceylan İ, Erden Z, Erçetin Ö. Zon 2 fleksör tendon yaralanmalarında Modifiye Duran Protokolünün klinik sonuçları. J Exercise Ther Rehabil 2018. 5: 150-7.
15. Flowers KR. String wrapping versus massage for reducing digital volume. Physical Ther 1988; 68: 57-9.
16. Miller LK, Jerosch-Herold C, Shepstone L. Effectiveness of edema management techniques for subacute hand edema: a systematic review. J Hand Ther 2017. 30: 432-46.
17. Seçkin Ü. Rehabilitation of the Tendon Injuries in the Hand. Türkiye Klinikleri J PM&R-Special Topics 2008; 1: 38-47.
18. Quinlan CS, Hevican C, Kelly JL. A useful dressing for isolated digit injuries. Eur J Orthopedic Surg Traumatol 2018; 28: 999-1000.
19. Güdemez E, Ataker Y, Cömert Ece S. El ve El Bileği Muayenesi, Kayıt Tutma, Fotoğraflama in El rehabilitasyonu. ed. Çerezci, Ö, Ataker, Y, Canbulat, N, Güdemez, E. Amerikan Hastanesi; 2013; 19-43
20. Hwang JH, Lee CH, Lee HH, Kim SY. A new soft tissue volüme measurement strategy using ultrasonography. Lymphatic Res Biol 2014; 12: 89-94.
21. Lowell M, Pirc P, Ward RS, et al. Effect of 3M™ Coban™ self adherent wraps on edema and function of the burned hand: a case study. J Burn Care Rehabil 2003; 24: 253-8.
22. Paker N, Alp M, Bardak AN, Buğdaycı D, Sabırlı F, Ersoy S. Evaluation of wrist range of motion and hand grip strength in women with the diagnosis of carpal tunnel syndrome: a controlled study. J Physical Med Rehabil Sci 2020; 23: 57-61
23. Duruöz MT, Poiraudeau S, Fermanıan J, Menkes C J. Development and validation of a rheumatoid hand functional disability scale that assesses functional hadicap. J Rheumatol 1996; 23: 1167- 72.
24. Dixon, J, and Bird, H. Reproducibility along a 10 cm vertical visual analogue scale. Annals of the Rheumatic Diseases 1981; 40: 87-9.
25. Demiral Y, Ergor G, Unal B, et al. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. BMC Public Health 2006; 6: 1-8.
26. Moffatt CJ, Franks PJ, Hardy D, Lewis M, Parker V, Feldman JL. A preliminary randomized controlled study to determine the application frequency of a new lymphoedema bandaging system. Bri J Dermatol 2012; 166: 624-32.
27. Lutsky KF, Giang EL, Matzon JL. Flexor tendon injury, repair and rehabilitation. Orthop Clinics 2015; 46: 67-76.
28. Frueh FS, Kunz VS, Gravestock IJ, et al. Primary flexor tendon repair in zones 1 and 2: early passive mobilization versus controlled active motion. J Hand Surg 2014; 39: 1344-50.
29. Kitis PA, Buker N, Kara IG. Comparison of two methods of controlled mobilisation of repaired flexor tendons in zone 2. Scand J Plastic Reconstruct Surg Hand Surg 2009; 43: 160 5.
30. Bircan C, El Ö, Akalın E, et al. Functional outcome in patients with zone V flexor tendon injuries. Arch Orthop Trauma Surg 2005; 125: 405-9.
31. Chan TK, Ho CO, Lee WK, Fung YK, Law YF, Tsang CY. Functional outcome of the hand following flexor tendon repair at the 'no man's land'. J Orthop Surg 2006; 14: 178-83.
32. Strickland JW, Glogovac SV. Digital function following flexor tendon repair in zone II: a comparison of immobilization and controlled passive motion techniques. J Hand Surg 1980; 5: 537-43.
33. Turan Y, Duruöz MT, Aksakallı E, Gürgan A. Validation of Duruöz Hand Index for diabetic hand dysfunction. J Invest Med 2009; 57: 887-91.
34. Erçalık T, Şahin F, Erçalık C, Doğu B, Dalgıç S, Kuran B. Psychometric characteristics of Duruoz Hand Index in patients with traumatic hand flexor tendon injuries. Disabil Reh 2011; 33: 1521-7.
35. Jonker L, Bell L, Robinson K, Davidson K, Dawson M. Application of compression bandaging post-osteotomy results in altered pain profile; results of a single-centre randomised controlled trial. Int J Orthop Trauma Nurs 2021; 42: 100833.
36. Lee M, Jung YR, Lee YK. Trigger finger secondary to a neglected flexor tendon rupture. Med 2019; 98: e13980.
37. Galasso O, Mariconda M, Donato G, et al. Histopathological, clinical, and electrophysiological features influencing postoperative outcomes in carpal tunnel syndrome. J Orthop Res 2011; 29: 1298-1304.
38. Oktayoğlu P, Acar A, Gündüz İ, Cağlayan M, Akbostancı, MC. Assessment of hand functions inpatients with idiopathic cervical dystonia. Human Movement Sci 2020; 70: 102581.

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Effectiveness of hydrodistention procedure under local anesthesia in the treatment of bladder pain syndrome/ interstitial cystitis

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ABSTRACT

Objective: We aimed to indicate the effectiveness of local anesthesia in the treatment of hydrodistention in women with Bladder Pain Syndrome/interstitial Cystitis (BPS/IC) in our study.

Material and Method: The data of a total of 77 female patients who underwent hydrodistention treatment for BPS/IC in our clinic between January 2015 and July 2021 were analyzed retrospectively. The patients were divided into two groups as local anesthesia (LA, n=41) and spinal anesthesia (SA, n=36) groups according to the type of anesthesia applied. The groups were compared by determining the preoperative and postoperative O'Leary symptom index (SI) and problem index (PI), minimum voiding volume (MinVV), maximum voiding volume (MaxVV), average voiding volume (AvgVV) and daily frequency.

Results: The mean age of the patients was 48.97±11.09 years in the LA group and 45.19±14.35 years in the SA group (p=0.197). There was no significant difference between the groups in terms of the preoperative European Society for the Study of Interstitial Cystitis (ESSIC) group (p=0.999). During the postoperative period, a median (IQR) improvement of 11.0 (2.0) points was observed in the SI of the LA group, while a median improvement of 11.0 (2.0) points were observed in the SA group (p=0.437). The median improvement in PI score was 8.4 (4.0) points in the SA group, while it was 7.0 (3.0) points in the LA group (p=0.415). There was no significant difference between the groups in terms of improvements in minVV, maxVV, avgVV and daily frequency (p=0.480, p=0.460, p=0.614 and p=0.910, respectively).

Conclusion: Hydrodistention treatment in women with BPS/IC can be performed safely and with high success rate under local anesthesia and it is well tolerated by the patients. Local anesthesia offers a minimally invasive treatment option as well as the advantage of avoiding possible complications of spinal, epidural or general anesthesia.

Keywords: Bladder pain, hydrodistention treatment, local anesthesia

INTRODUCTION

Bladder pain syndrome/Interstitial cystitis (BPS/IC) is a chronic disease characterized by the presence of persistent irritating micturition symptoms and chronic pain felt in the pelvic region (1). According to the most accepted theory, BPS/IC is developed due to a primary damage of the glycosaminoglycan (GAG) layer in the bladder urethelium (2). It significantly reduces the quality of life in patients due to depression, anxiety, insomnia, fatigue, dyspareunia and several sexual problems (3). According to the definition of European Society for the Study of Interstitial Cystitis (ESSIC) BPS/IC is characterized by chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or urinary frequency ,and establishes a list of confusable diseases that must be excluded. With this definition, ESSIC recommends diagnostic cystoscopy and cystoscopy-guided biopsy and hydrodistention treatment, and grades BPS/IC based on these findings (4). The European Association of Urology (EAU) committee also approves this definition made by ESSIC and recommends hydrodistention treatment during cystoscopy (5). Hydrodistention performed during cystoscopy provides simultaneous diagnosis and treatment in patients with suspected BPS/IC, as well as facilitating the exclusion of other possible bladder pathologies. Hydrodistention during cystoscopy is classically performed under general, spinal

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or epidural anaesthesia. However, this situation not only increases the possible risks that may develop secondary to general anesthesia, but also leads to more hospitalization and loss of work. Therefore, performing the procedure under local anesthesia provides the patient with a more minimally invasive treatment option and provides the advantage of preventing risks that may develop secondary to spinal, general or epidural anesthesia (6). Lidocaine that instilled into the bladder before cystoscopy suppresses pain secondary to bladder tension by reducing c-fiber activity and allows hydrodistention (7). According to our literature research, it was obtained that there are very limited studies on the application of cystoscopy and hydrodistention under local anesthesia. In addition, it has been determined that there is not enough data in the literature regarding the comparative results of hydrodistention treatment performed under local anesthesia with hydrodistention performed under spinal or general anesthesia. Therefore, in the present study, we aimed to exhibit the efficacy and safety of hydrodistention treatment performed under local anesthesia by comparing the results of hydrodistention treatment performed under local anesthesia and spinal anesthesia in our clinic.

MATERIAL AND METHOD

Preoperative Evaluation

After the study approval was obtained from the ethics committee of Health Sciences University Keçiören Training and Research Hospital (Date:14.09.2021, No: 2012-KAEK-15/2369), the data of 77 female patients who were treated for hydrodistention due to BPS/IC in our clinic between January 2015 and July 2021 were retrospectively analyzed. All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration. Patients with urgency, pollakiuria (>7 urination in a 24-h period) and painful bladder symptoms for at least 6 months and who did not benefit from conservative treatment methods were included in the study. However, patients with a history of bladder outlet obstruction, bladder tumor, bladder stone, active urinary tract infection in urine culture, post-void residual urine volume (PVR) >50 ml, or neurogenic bladder were excluded from the study. In addition, those with an active vaginitis, endometriosis or uro-gynecological disorder such as cystocele, rectocele or severe stress urinary incontinence that will require surgery were also excluded from the study.

A detailed physical examination, including vaginal examination were performed following the clinical histories of the patients. Routine urinalysis, urine culture, urea, creatinine values, uroflowmetry and PVR measurements and urinary system ultrasonography of all patients were recorded. Symptom index (SI) and problem index (PI) scores were determined by evaluating all patients symptomatically using the O'Leary Sant questionnaire scale (8). In addition, the minimum voided volume (minVV), maximum voided volume (maxVV), average voided volume (avgVV) and 24-h frequency values of the patients were defined in detail. PI and SI scores, voided volume and 24-h frequency values were determined and recorded in the 3rd month following the procedure. The patients were divided into two groups as local anesthesia (LA, n=41) group and spinal anesthesia (SA, n=36) group according to the anesthesia type in which the procedure was performed.

Cystoscopy and Hydrodistention Procedure

Cystoscopy and simultaneous hydrodistention were performed in both groups using a 21 Fr rigid cystoscope (Olympus) and 30 degree optics. The glomerulation grade of the bladder was evaluated according to the criteria of the interstitial cystitis database study (9) and cold-cup biopsy was taken during cystoscopy if necessary. The ESSIC groups of the patients were determined according to the glomerulation grade, cystoscopy findings and biopsy criteria.

In the SA group, the bladder was filled with saline infusion and waited for 10 minutes until changes in the bladder mucosa were observed in routine cystoscopy. During the procedure, saline infusion was made at a height of approximately 80 cm from the patient with physiological flow. Subsequently, the bladder was emptied and a 16-18 Fr foley catheter was placed into the bladder and the procedure was terminated. All patients in the SA group were discharged on the 1st postoperative day following their urethral catheters removed. In order to provide an adequate local anesthesia for the procedure in LA group, 10 ml of 4% lidocaine was diluted with 40 ml of saline and instilled into the bladder using a 16 or 18 Fr foley catheter. In this way, the optimum local anesthetic effect sufficient for the procedure was obtained by waiting for about 10 minutes. Following local anesthesia, saline infusion was started to physiological flow from a height of approximately 80 cm to the patients and the infusion was continued until the pain level that the patients could tolerate a maximum degree during bladder filling. At the point where the patients could not tolerate the pain, the infusion was terminated and the amount of saline infused was recorded. Afterwards, the bladder was emptied and the procedure was terminated. No urethral catheter was inserted after the procedure in the patients in the LA group. The patients in the LA group were discharged after being followed up in the outpatient clinic observation room for approximately two hours. SI, PI, maxVV, minVV, avgVV and 24-h frequency values of the patients were determined before the procedure and at the 3rd month after the procedure, and the groups were compared.

Statistical Analysis

All statistical analyses were performed using the SPSS 24.0 (IBM Corp., Chicago) software for Windows. ''Freguencies" and ''descriptives" was used for descriptive statistics. For a normal distribution independent samples-t test was used as means and standart deviation. In the univariate analysis, Chi-Square Test was used for nominal data, while the Mann-Whitney U test was used for nonparametric variables. Median (minimum-maximum) or median (Interquartile range) were used for continuous data. A p-value of <0.05 was considered as statistically significant.

RESULTS

The mean age of the patients was 48.97±11.09 years in the LA group,while it was 45.19±14.35 years in the SA group (p=0.197). According to the preoperative cystoscopy findings, the glomerulation grades of the LA and SA groups were found to be similar (Grade 0=9/5, Grade 1=17/22, Grade2=11/5 and Grade 3=4/4, p=0.293). Similarly, there was no significant difference between the groups in terms of preoperative ESSIC groups (p=0.999) (**Table 1**). While the preoperative median (IQR) O'Leary SI score of the LA group was 15.0 (2.50) points, it was 15.5 (2.75) points in the SA group (p=0.942). The median preoperative O'Leary PI score was 11.0 (3.50) points in the LA group and it was 12.5 (3.75) points in the SA group (p=0.093). There was no significant difference between the groups in terms of preoperative minVV, maxVV, avgVV and daily frequency (p=0.413, p=0.639, p=0.822 and p=0.305, respectively) (**Table 2**). In the evaluation performed at the 3rd month following hydrodistention, the median O'Leary SI score of the LA group was 5.0 (3.0) points, while the SI score of the SA group was similarly 5.0 (3.0) points (p=0.934). The postoperative median O'Leary PI score was 3.0 (2.0) in the LA group, while it was 4.0 (2.0) in the SA group (p=0.298). Similarly, no significant difference was found between the groups in terms of postoperative minVV, maxVV, avgVV and daily frequency (p=0.245, p=0.524, p=0.560 and p=0.315, respectively) (**Table 3**). A median 11.0 (2.0) point improvement was found in the LA group in the O'Leary SI score in the postoperative 3rd month, while there was a similar improvement of 11.0 (2.0) points in the SA group (p=0.437). It was also observed that there was no significant difference between the groups in terms of improvement in O'Leary PI scores (LA=7.0 (3.0) points vs SA=8.4 (4.0) points and p=0.415). While an average improvement of 60.7±29.6 ml was observed in the minVV of the LA group, it was 66.3±40.0 ml in the SA group (p=0.480). Similarly, there was no significant difference between the LA and SA groups in terms of mean improvement in maxVV and mean improvement in avgVV (160.0±80.0 ml vs 156.5±70.5ml and 116.0±62.7 ml vs 113.6±78.3 ml, p=0.460 and p=0.614, respectively). In addition, it was observed that the median improvement in daily frequency in the LA group was 7.0 (3.5) ,while it was 7.0 (3.0) in the SA group, and there was no significant difference between the groups (p=0.910) (**Table 4** and **Figure 1**).

Table 1. Preoperative patient's characteristics according to groups

	Local (n=41)	Spinal (n=36)	p
Age, mean±SD, years	48.97±11.09	45.19±14.35	0.197
Glomerulation grade, n (%)			0.293
Grade 0	9 (22.0)	5 (13.9)	
Grade 1	17 (41.5)	22 (61.1)	
Grade 2	11 (26.8)	5 (13.9)	
Grade 3	4 (9.8)	4 (11.1)	
ESSIC group, n (%)			0.999
1X	4 (9.8)	3 (8.3)	
1A	6 (14.6)	5 (13.9)	
1B	3 (7.3)	4 (11.1)	
1C	6 (14.6)	5 (13.9)	
2A	3 (7.3)	2 (5.6)	
2B	6 (14.6)	7 (19.4)	
2C	9 (22.0)	7 (19.4)	
3A	3 (7.3)	2 (5.6)	
3B	1 (2.4)	1 (2.8)	

*SD: Standard deviation, ESSIC: European Society for the Study of Interstitial Cystitis

Table 2. Preoperative O'Leary scores and voiding parameters of the groups

	Local (n=41)	Spinal (n=36)	p
Semptom index, median (IQR)	15.0 (2.50)	15.5 (2.75)	0.942
Problem index, median (IQR)	11.0 (3.50)	12.5 (3.75)	0.093
Minimum voided volum, median (IQR), ml	50.0 (30.0)	50.0 (40.0)	0.413
Maximum voided volum, median (IQR), ml	200.0 (65.0)	200.0 (107.5)	0.639
Average voided volum, median (IQR), ml	130.0 (42.5)	127.5 (63.75)	0.822
Daily frequency, median (IQR)	15.0 (3.5)	14.0 (4.0)	0.305

*IQR: Interquartile range, SD: Standard deviation

Table 3. Postoperative O'Leary scores and voiding parameters of the groups

	Local (n=41)	Spinal (n=36)	p
Semptom index, median (IQR)	5.0 (3.0)	5.0 (3.0)	0.934
Problem index, median (IQR)	3.0 (2.0)	4.0 (2.0)	0.298
Minimum voided volum, median (IQR), ml	120.0 (65.0)	145.0 (107.5)	0.245
Maximum voided volum, mean±SD, ml	365.3±64.7	356.7±69.9	0.524
Average voided volum, mean±SD, ml	253.6±66.6	244.5±64.8	0.560
Daily frequency, median (IQR)	7.0 (3.5)	7.0 (1.0)	0.315

*IQR: Interquartile range, SD: Standard deviation

Table 4. Improvement in O'Leary scores and voiding parameters of the groups

	Local (n=41)	Spinal (n=36)	p
Semptom index, median (IQR)	11.0 (2.0)	11.0 (2.0)	0.437
Problem index, median (IQR)	7.0 (3.0)	8.4 (4.0)	0.415
Minimum voided volum, mean±SD, ml	60.7±29.6	66.3±40.0	0.480
Maximum voided volum, mean±SD, ml	160.0±80.0	156.5±70.5	0.460
Average voided volum, mean±SD, ml	116±62.7	113.6±78.3	0.614
Daily frequency, median (IQR)	7.0 (3.5)	7.0 (3.0)	0.910

*IQR: Interquartile range, SD: Standard deviation

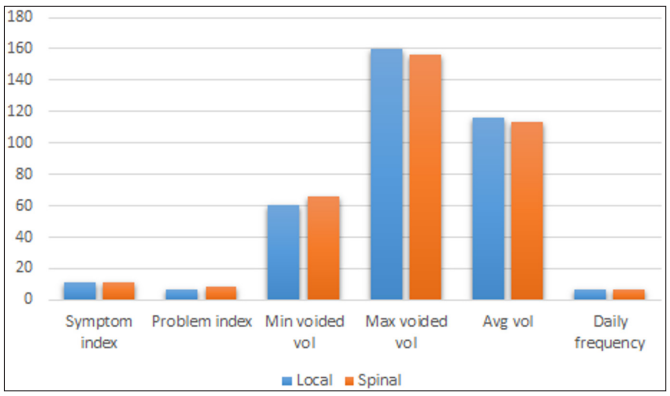

Figure. Improvement in O'Leary scores and voiding parameters of the groups

DISCUSSION

Currently, due to the increase in the number of patients diagnosed BPS/IC, more studies are being conducted on different treatment modalities of the disease and the application forms of treatment vary. In addition, due to its negative effects on working life, depression, anxiety, chronic pain and sexual dysfunctions, especially in women, cause a significant decrease in the quality of life (10). Recent studies have drawn attention to the fact that BPS/IC seriously increases the rate of depression and anxiety in the chronic period, and therefore it is important to initiate treatment in the early period (11). Historically, various protocols have been applied in the treatment of BPS/IC, primarily medical therapy and intravesical instillation. Hydrodistention treatment was first applied by Dunn et al. (12) in 1977. Hydrodistention concomitant with cystoscopy is not only therapeutic, but also offers the advantage of excluding other bladder diseases and taking a simultaneous biopsy if necessary. Although the ESSIC and EAU guidelines recommend diagnostic and therapeutic hydrodistention in patients with BPS/IC, they do not offer any recommendations on procedural technique (4,5). On the other hand, AUA recommends that the hydrodistention procedure be performed under general, spinal or epidural anesthesia, for less than 10 minutes and under a low pressure of 60-80 cmH_2O (13). In line with these recommendations, in our study, saline infusion was applied into the bladder from a height of 80 cm from the patient and the infusion time did not exceed 10 minutes.

Until today, hydrodistention treatment has been performed under spinal, epidural or general anesthesia in many centers and successful results have been reported. In a study conducted by Yamada et al. (14) which included 52 patients, it was reported that hydrodistention treatment under epidural anesthesia was 70% effective for more than three months and no serious complications were encountered. In another review study conducted by Ens et al. (15) it was reported that hydrodistention treatment provided 54% to 90% symptomatic relief within 6 to 9 months and no serious complications were observed in similar studies. Ahmad et al. (16) reported that after hydrodistention and intravesical hyaluronic acid (40 mg/50ml) treatment administered under general anesthesia in a total of 23 patients, they found immediate improvement in the symptoms of 17 (74%) of the patients. In the same study, they were indicated that the healing of ulceration and resolution of inflammation were occurred in all responders. Similar to the literature data, significant improvement was found in the O'Leary SI and O'Leary PI scores of the local and spinal anesthesia groups at the end of the third month in our study, and no difference was found between the groups in terms of improvement scores.

Although many cystoscopic interventions have historically been successfully performed under general, spinal or epidural anesthesia, urologists have managed to perform many cystoscopic procedures under local anesthesia in order to perform these procedures more minimally invasive (17-19). Offiah et al. (20) performed intravesical lidocaine instillation in a total of 24 female patients with BPS and investigated whether the symptoms have a peripheral versus central mechanism. According to this study,there was a statistically significant volume increase following lidocaine treatment: maximal cystometric capacity (MCC) 192–261 ml post lidocaine (p=0.005.) In another study, Aihara et al. (21) reported the results of hydrodistention treatment administered under local anesthesia to a total of 30 patients, 27 of whom were women and 3 were men. In this study, it was reported that the patients could tolerate hydrodistention treatment well under local anesthesia and that all patients could be infused with >200 ml of saline. In addition, in the same study, they emphasized that 21/30 (71%) patients benefited from the treatment one month after the treatment, and significant improvement was found in the O'Leary SI and O'Leary PI scores ($p<0.0001$ and $p<0.0001$, respectively). According to

the same study, a median 60 ml increase in minVV, 55 ml in maxVV and 60 ml increase in avgVV was detected in the postoperative third month ($p<0.0001$, $p<0.0005$ and $p<0.0001$, respectively), and in addition, a median 4.5 (0-11) time decrease has been reported in 24-h urinary frequency ($p<0.0001$). In our study, the results of hydrodistention treatment applied under local anesthesia and spinal anesthesia were compared. In our study, no significant difference was found between local and spinal anesthesia groups in terms of improvement in O'Leary SI and O'Leary PI scores. In addition, there was no significant difference between the groups in terms of median increase in minVV, maxVV, avgVV and the median decrease in daily voiding frequency. Our outcomes are consistent with the literature data, and no serious complications such as severe bleeding, bladder perforation or hypersensitivity reaction secondary to local anesthesia were observed in any patient. These results support the idea that hydrodistention therapy can be effective and safely performed under local anesthesia. Hydrodistention treatment performed under local anesthesia provides similar improvement rates that performed under spinal anesthesia.

The most important limitation of our study is its retrospective nature. In addition to the results at the end of the third month, the absence of long-term follow up results is another important limitation. On the other hand, because the VAS pain scores of the groups were not obtained in the early postoperative period, the fact that the groups were not compared in terms of postoperative pain scores can be considered as another limitation.

CONCLUSION

The results of hydrodistention treatment performed under local anesthesia are similar to hydrodistension treatment performed under spinal anesthesia. The procedure performed under local anesthesia provides similar improvement rates to that performed under spinal anesthesia in terms of the increase in the patients' O'Leary SI, O'Leary PI and voiding volumes, as well as the decrease in daily voiding frequency. Local anesthesia avoids the possible complications of spinal or general anaesthesia, allowing hydrodistention to be performed at less cost and with minimal working loss. However, the hypersensitivity reaction that may develop secondary to local anesthesia should be kept in mind, and it should be known that additional spinal or general anesthesia may be needed in cases where the patient cannot tolerate the procedure due to pain. There is a need for randomized controlled studies that compare the local anesthesia with spinal, epidural or general anesthesia and include longer follow-up periods in this respect.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Health Sciences University Keçiören Training and Research Hospital Ethics Committee (Date:14.09.2021, Decision No: 2012-KAEK-15/2369).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

REFERENCES

1. Hanno P, Dmochowski R. Status of international consensus on interstitial cystitis/bladder pain syndrome/painful bladder syndrome: 2008 snapshot. Neurourol Urodyn 2009; 28: 274-86.
2. Parsons CL. The therapeutic role of sulfated polysaccharides in the urinary bladder. Urol Clin North Am 1994; 21: 93-100.
3. Bogart LM, Suttorp MJ, Elliott MN, Clemens JQ, Berry SH. Validation of a quality-of-life scale for women with bladder pain syndrome/interstitial cystitis. Qual Life Res 2012; 21: 1665-70.
4. van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 2008; 53: 60-7.
5. Engeler D, Baranowski AP, Borovicka J, et al. Guidelines on Chronic Pelvic Pain. The Annual EAU Congress. Spanish, 2015. Available online: http: /uroweb.org/guideline/ chronic-pelvic-pain.
6. Thrasher JB, Kreder KJ, Peterson NE, Donatucci CF. Lidocaine as topical anesthesia for bladder mappings and cold-cup biopsies. J Urol 1993; 150: 335-6.
7. Teichman JM, Nielsen-Omeis BJ, McIver BD. Modified urodynamics for interstitial cystitis. Tech Urol 1997; 3: 65-8.
8. O'Leary MP, Sant GR, Fowler FJ Jr, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. Urology 1997; 49: 58-63.
9. Nigro DA, Wein AJ, Foy M, et al. Associations among cystoscopic and urodynamic findings for women enrolled in the Interstitial Cystitis Data Base (ICDB) Study. Urology 1997; 49: 86-92.
10. El Khoudary SR, Talbott EO, Bromberger JT, Chang CC, Songer TJ, Davis EL. Severity of interstitial cystitis symptoms and quality of life in female patients. J Womens Health (Larchmt) 2009; 18: 1361-8.
11. Nickel JC, Kaufman DM, Zhang HF, Wan GJ, Sand PK. Time to initiation of pentosan polysulfate sodium treatment after interstitial cystitis diagnosis: effect on symptom improvement. Urology 2008; 71: 57-61.
12. Dunn M, Smith JC, Ardran GM, Ramsden P. Urgency and urge incontinence of urine treated by prolonged bladder dystension: interim results. Urol Int 1977; 32: 107-13.

13. Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011; 185: 2162-70.
14. Yamada T, Murayama T, Andoh M. Adjuvant hydrodistension under epidural anesthesia for interstitial cystitis. Int J Urol 2003; 10: 463-8.
15. Ens G, Garrido GL. Role of cystoscopy and hydrodistention in the diagnosis of interstitial cystitis/bladder pain syndrome. Transl Androl Urol 2015 ; 4: 624-8.
16. Ahmad I, Sarath Krishna N, Meddings RN. Sequential hydrodistension and intravesical instillation of hyaluronic acid under general anaesthesia for treatment of refractory interstitial cystitis: a pilot study. Int Urogynecol J Pelvic Floor Dysfunct 2008; 19: 543-6.
17. Ströck V, Holmäng S. Is bladder tumour fulguration under local anaesthesia more painful than cystoscopy only? Scand J Urol 2020; 54: 277-80.
18. Fabuel Alcañiz JJ, Martínez Arcos L, Jimenez Cidre M, Burgos Revilla FJ. Toxina botulínica intravescal con anestesia local como procedimiento ambulante (Intravesical botulinum toxin under local anestesia as ambulatory procedure). Arch Esp Urol 2017; 70: 635-44.
19. Syed HA, Talbot N, Abbas A, et al. Flexible cystoscopy and Holmium: Yttrium aluminum garnet laser ablation for recurrent nonmuscle invasive bladder carcinoma under local anesthesia. J Endourol 2013; 27: 886-91.
20. Offiah I, Dilloughery E, McMahon SB, O'Reilly BA. Prospective comparative study of the effects of lidocaine on urodynamic and sensory parameters in bladder pain syndrome. Int Urogynecol J 2019 ; 30: 1293-301.
21. Aihara K, Hirayama A, Tanaka N, Fujimoto K, Yoshida K, Hirao Y. Hydrodistension under local anesthesia for patients with suspected painful bladder syndrome/interstitial cystitis: safety, diagnostic potential and therapeutic efficacy. Int J Urol 2009; 16: 947-52.

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Office-based management of Bartholin cysts and abscesses: a comparison of three surgical methods

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ABSTRACT

Aim: In the present study, we aimed to compare the effectiveness of incision + drainage alone, marsupialization, and incision + drainage followed by silver nitrate application for the office management of Bartholin cysts/abscesses.

Material and Method: A total of 128 women who presented to our clinic, diagnosed with Bartholin cysts/abscesses and underwent Bartholin gland sparing office-based surgery were included in this retrospective study. Patients' demographic data, laterality and size of the cyst, surgical method performed, operational time, presence of recurrence, and treatment method of recurrent cysts/abscesses were recorded. Patients were divided into three group according to the operation they have undergone as incision + drainage alone, incision + drainage followed by silver nitrate, marsupialization.

Results: The mean cyst diameter was found as 3.00±1.05 cm. Eighteen (14.1%) patients developed recurrence. Of all patients, 37.5% underwent incision + drainage alone, 8.6% incision + drainage followed by silver nitrate application and 62.5% marsupialization. The mean operational time was significantly longer in the marsupialization group compared to incision + drainage alone and incision + drainage followed by silver nitrate groups (both, $p<0.001$). None of the patients in the marsupialization group developed recurrence, while recurrence was observed in 35.1% of the patients in the incision + drainage and 45.5% of the patients in the incision drainage + silver nitrate group.

Conclusion: Marsupialization technique was superior over the other techniques in terms of recurrence. However, operational time was longer with this technique and no definitive conclusion could be drawn.

Keywords: Bartholin cyst, abscess, infusion, drainage, marsupialization

INTRODUCTION

Bartholin cysts/abscesses are a benign obstruction of the Bartholin glands that are located in the lower right and left portions of the vaginal introitus. These are relatively frequent pathologies of the vulva and vagina that may cause discharge, pain and dyspareunia (1). A Bartholin abscess usually occurs after onset of puberty and decreases in incidence following menopause (2). It is generally unilateral and asymptomatic, and most of these abscesses are detected incidentally with imaging investigations or at a physical exam. However, when symptomatic, these abscesses may cause dyspareunia, urinary irritation, vague pelvic pain and restrictions in daily activities. Symptomatic Bartholin cysts/abscesses account for approximately 2% of gynecologic visits each year (3).

The physical exam often reveals asymmetry inferior to the vulva. In general, Bartholin cysts/abscesses do not require laboratory and imaging studies. However, biopsy and wound cultures may be performed during incision and drainage of the abscess, especially when malignancy is suspected (4). Differential diagnosis may include vaginal prolapse, endometriosis, perineal leiomyoma, fibroma, hematoma, folliculitis and other cysts of the vulva (5).

Bartholin abscesses can be treated with several medical or surgical methods at office settings. Office management of these abscesses is determined by the patient's age, cyst size, and history of recurrence (6). When medication fails or upon patient's request, several minor surgical techniques are applied to treat Bartholin cysts/abscesses. Commonly performed office-based minor surgical techniques include incision+drainage alone, alcohol sclerotherapy, Jacobi ring fistulization, marsupialization, needle aspiration, incision+drainage + silver nitrate, and Word catheter fistulization (7). Each of these techniques has its own advantages and disadvantages, and none of them has been proven superior in terms of healing time

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and recurrence. Incision + drainage alone and needle aspiration techniques are relatively simple procedures that can be performed in a short time, but have a higher rate of recurrence (8, 9). Alcohol sclerotherapy shows a faster healing time, but it is associated with the risk of developing hyperemia, hematoma, tissue necrosis and scarring (10). Marsupialization is associated with a lower risk of recurrence, while it takes longer time to perform and is more costly (11). Silver nitrate therapy has a shorter treatment time, although it is associated with scarring, vulvar burning, labial edema and hematoma (12). There is no consensus in the literature on which of these methods is superior over the others in treatment of Bartholin cysts/abscesses. In the present study, we aimed to compare the effectiveness of incision + drainage alone, marsupialization, and incision + drainage followed by silver nitrate application for the office management of Bartholin cysts/abscess.

MATERIAL AND METHODS

The study was carried out with the permission of Liv Hospital Ethics Committee (Date: 01.10.2021, Decision No: 2021/002). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 128 women who presented to our clinic with the complaints of pain, dyspareunia, discharge and restricted movements, diagnosed with Bartholin cysts/abscesses and underwent Bartholin gland sparing office-based surgery between 2018 and 2021 were included in this retrospective study. Symptomatic patients who had a cyst/abscess with the longest axis ≤ 5 cm were enrolled. Patients who previously received treatment for Bartholin cysts/abscesses in an outer center, those with a longest cyst axis >5 cm, patients who received medical therapy alone, and those with missing data were excluded from the study.

Study data were obtained via the hospital information system and patient files, and retrospectively analyzed. Patients' age, body mass index (BMI), complaints at the time of admission, laterality and size of the cyst, sexual activity status, history of pregnancy, delivery mode, surgical method performed, operational time, presence of recurrence, and treatment method of recurrent cysts/abscesses were recorded. Recurrence was evaluated 12 months after the initial treatment during control visits. Patients were divided into three groups according to the operation they have undergone as incision + drainage alone (Group ID), marsupialization (Group M), and incision + drainage followed by silver nitrate (Group IDSN), and the study data were compared between the groups.

Surgical Technique

All procedures were performed by the same team under local anesthesia with the patients in the lithotomy position. In the Group ID, after cleaning the surgical site with antiseptic iodine, local anesthesia was applied with 2% lidocaine superior to the hymen ring, and the drainage of the cyst was then provided through an incision of 3-5 mm. In the Group IDSN first, the same procedure with Group ID was performed for the drainage and a 0.5x0.5 cm silver nitrate (AgNO3) patch was applied on the cyst wall through the incision for ablation. In the group M, an incision was made in the area where the cyst protruded to the vestibule out of the hymen ring. The cyst wall was everted and approximated to the edge of the vestibular mucosa with interrupted absorbable sutures (3-0 Vicryl) using a fine needle. Patients were called one week later to clean the necrotic tissues.

Statistical Analysis

Data obtained in this study was statistically analyzed using IBM SPSS Statistics version 26.0 (SPSS, Statistical Package for Social Sciences, IBM Inc., Armonk, NY, USA) software. Categorical variables were expressed with frequencies (number, percentage) and numerical variables with descriptive statistics (mean ± standard deviation). Normality of the numerical data was analyzed using Kolmogorov-Smirnov test and the variables were found to have a normal distribution. Therefore, parametric statistical methods were used in the analysis.

Differences between two groups were analyzed with the Independent sample t test, while the differences between more than two groups were evaluated with the One Way Variance Analysis (ANOVA). In the case of difference with ANOVA, Tukey multiple comparison test was used to determine the group, which created the difference. Correlations between two numerical variables were evaluated with Pearson's correlation analysis and the correlations between two categorical variables with Chi-square test. $p<0.05$ values were considered statistically significant.

RESULTS

A total of 128 women with Bartholin cysts/abscesses were included in the study. The mean age of the patients was 36.91±8.41 years. The mean BMI value was calculated as 24.68±3.22 Kg/m². The mean operational time was measured as 29.38±15.83 minutes. Bartholin cysts/abscesses were at the right side in 61 (47.7%), at the left side in 63 (49.2%) and bilateral in 4 (3.1%) patients. The mean cyst diameter was found as 3.00±1.05 cm. Eighteen (14.1%) patients developed recurrence. A total of 102 (79.69%) women had a history of pregnancy, while 26

(20.31%) women were nulligravida. The number of sexually active women was 105 (82.00%). Demographic and clinical features of the patients are given in **Table 1**.

The most common complaints during admission was a palpable mass (89.8%) followed by pain (78.9%), dyspareunia (59.4%), discharge (25%), while 19.5% of the patients were asymptomatic. Of all patients, 48 (37.5%) underwent incision + drainage alone (Group ID), 11 (8.6%) incision + drainage followed by silver nitrate application (Group IDSN) and 80 (62.5%) marsupialization (Group M).

Table 1. Demographic and clinical features of the patients with Bartholin cysts/abscesses

	Mean	± SD
Age (year)	36.91	8.41
BMI (Kg/m²)	24.68	3.22
Operational time (minutes)	29.38	15.83
	Number	**%**
Laterality		
Right	61	47.7
Left	63	49.2
Bilateral	4	3.1
Cyst size		
1-2 cm	44	34.4
2.1-3 cm	37	28.9
3.1-5 cm	47	36.7
Sexual Activity		
Yes	105	82.0
No	23	18.0
Vaginal delivery		
Yes	73	57.0
No	55	43.0
C/S		
Yes	38	29.7
No	90	70.3
Recurrence		
Yes	18	14.1
No	110	85.9

C/S: cesarean section; BMI: Body Mass Index; SD: standard deviation

Study parameters were compared between the three groups. The mean age was found as 37.15±8.09 years in Group M, 37.16±9.54 years in Group ID and 34.36±6.90 years in Group IDSN. There was no statistically significant difference between the groups in terms of age (p=0.579). The mean BMI value was statistically significantly higher in Group ID compared to Group M (25.57±3.07 vs 24.06±3.15) (p=0.015). The mean operational time was measured as 37.13±10.34 minutes in Group M, 13.57±5.42 minutes in Group ID and 26.18±8.00 in Group IDSN. Accordingly, the mean operational time was significantly longer in Group M compared to Group ID and Group IDSN (both, p<0.001). In addition, the mean operational time was significantly lower in Group ID compared to Group IDSN (p<0.001) (**Figure 1**). No statistically significant difference was observed between the three groups in terms of the other parameters. Comparison of the demographic and clinical features between the groups are shown in **Table 2.**

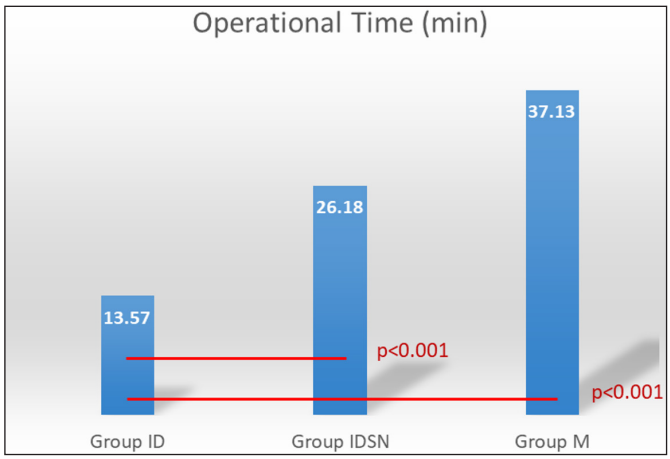

Figure 1. Operational duration according to the groups

Table 2. Comparison of the demographic and clinical parameters according to the groups

	Group M	Group ID	Group IDSN	F	p
	Mean±SD	Mean±SD	Mean±SD		
Age (years)	37.15±8.09	37.16±9.54	34.36±6.90	0.549	0.579
BMI (Kg/m²)	24.06±3.15	25.57±3.07	26.19±3.31	4.230	0.015
Operational Time (minutes)	37.13±10.34	13.57±5.42	26.18±8.00	87.333	<0.001
	n (%)	n (%)	n (%)	X2	p
Normal delivery				4.557	0.102
Yes	49 (61.3)	21 (56.8)	3 (27.3)		
No	31 (38.8)	16 (43.2)	8 (72.7)		
C/S				0.035	0.983
Yes	24 (30.0)	11 (29.7)	3 (27.3)		
No	56 (70.0)	26 (70.3)	8 (72.7)		
Recurrence				36.656	<0.001
Yes	0 (0.0)	13 (35.1)	5 (45.5)		
No	80 (100.0)	24 (64.9)	6 (54.5)		

Group M: Group marsupializaton, Group ID:Group incision drainage Group IDSN: Group incision drainage plus silver nitrate; C/S: cesarean section; BMI: Body Mass Index; SD: standard deviation.

As seen in **Table 2**, 13 (35.1%) patients in Group ID and 5 (45.5%) patients in Group IDSN developed recurrence, while none of the patients in Group M developed recurrence of Bartholin cysts/abscesses. The rate of recurrence was found to be statistically significantly lower in Group M than the other groups. Group ID and Group IDSN were not compared for recurrence because of the small number of patients in Group IDSN.

DISCUSSION

Office management of Bartholin cysts/abscesses can be performed using both medical and minor surgical methods. The main goal of minor surgical procedures is to provide the best treatment outcomes and to increase patients' quality of life by sparing Bartholin glands that are critical structures in the female anatomy with providing lubrication of the vagina for sexual functioning. However, no ideal surgical option could be determined so far among several methods including incision+drainage, silver nitrat fustulization, marsupialization, Word catheter, alcohol sclerotherapy and newer laser techniques (13).

In the present study, we aimed to investigate the effectiveness of incision+drainage, incision+drainage with silver nitrate and marsupialization in 128 women. The risk of developing Bartholin cysts/abscesses increases after 30 years of old (7). In our study, the mean age was found as 36.91±8.41 years. Krissi et al. (14) reported the mean age as 33.5±12.1 years in patients diagnosed with acute Bartholin abscess. Riche et al. (15) reported the mean age as 36.00±11.8 years. In this respect, our finding was in the range reported in the literature.

The preferred office-based minor surgical treatment method varies among countries and healthcare centers, and is determined by the patient's age, cyst size, symptoms, patient's preference and the surgeon's discrete (6). In a survey study among surgeons from French university hospitals, the most commonly used method was reported as incision drainage by 87% and marsupialization by 13%. The participants stated that incision drainage is a simpler technique with shorter operational time, but the rates of complications and recurrence with this technique are yet to be clearly determined (16).

In our study, incision drainage was performed in 37.5%, incision drainage + silver nitrate in 8.6% and marsupialization in 62.5% of the patients. The most important result of the present study was the significant differences between the three techniques in terms of recurrence rates. In the present study, none of the patients in the marsupialization group developed recurrence, while the rate of recurrence was found as 45.5% in the incision drainage + silver nitrate group and 35.1% in the incision drainage group. However, the incision drainage + silver nitrate group included only 11 patients, making interpretation of this result difficult. In a prospective randomized controlled study, Ozdegirmenci et al. performed incision drainage + silver nitrate in 76 and marsupialization in 83 patients. The authors found similar recurrence rates between the two techniques and concluded that silver nitrate application is as effective as marsupialization (17). Kroase et al. reported the recurrence rate as 10.3% with marsupialization and 12.2% with Word catheter method after one years of the primary treatment (11). Mungan et al. found no recurrence in their patients with silver nitrate at the end of a 2-year follow-up period (18). Cho et al. and Haider et al. also found no recurrence in their patients with marsupialization as in our study (1, 19). In their cohort study with 320 patients treated with either Word catheter or marsupialization for Bartholin cysts/abscesses, Rotem et al. reported that 54 patients presented to the emergency department due to recurrence, but no correlation could be find with the recurrence and surgical technique (20).

Recurrence rates following different ofis-based minor surgical techniques used for the treatment of Bartholin cysts/abscesses vary widely among the studies. However, as mentioned above, a significant portion of the studies found similar recurrence rates between the techniques used. We strongly suggest that recurrence following treatment of these cysts/abscesses may be resulted from several factors other than the technique used for the treatment. In our study, marsupialization was the most successful technique for this purpose with the lowest rate of recurrence, but it is well-known that this method takes a longer time to perform and is more expensive compared to the others, indicating the need for further more comprehensive prospective randomized controlled studies to draw more definitive conclusions.

Study Limitations

The most important limitation of this study is its retrospective and single-center design. In addition, other postoperative complications such as hematoma, pain and dyspareunia could not be studied. Furthermore, the small number of patients in the incision drainage + silver nitrate group, made the comparison of recurrence rates with this technique difficult. The strength of this study was the relatively high total number of patients.

CONCLUSION

In terms of recurrence rates, marsupialization technique is superior over incision drainage alone and incision drainage plus silver nitrate methods in the treatment of Bartholin cysts/abscesses. However, operational time is longer with this technique and its long-term complications are not clear. Further comprehensive

studies with a larger series of patients are needed to provide contribution to the literature for establishing a consensus about which surgical method is the best choice for treatment of these cysts/abscesses.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Liv Hospital Ethics Committee (Date: 01.10.2021, Decision No: 2021/002).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Haider Z, Condous G, Kirk E, Mukri F, Bourne T. The simple outpatient management of Bartholin's abscess using the word catheter: a preliminary study. Aust N Z J Obstet Gynaecol 2007; 47: 137–40.
2. Lee WA, Wittler M. Bartholin Gland Cyst 2020 Nov 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
3. Marzano DA, Haefner HK. The bartholin gland cyst: past, present, and future. J Low Genit Tract Dis 2004; 8: 195-204.
4. Yuk JS, Kim YJ, Hur JY, Shin JH. Incidence of Bartholin duct cysts and abscesses in the Republic of Korea. Int J Gynaecol Obstet 2013; 122: 62-4.
5. Tavares KADS, Moscovitz T, Tcherniakovsky M, Pompei LM, Fernandes CE. Differential Diagnosis between Bartholin Cyst and Vulvar Leiomyoma: Case Report. Rev Bras Ginecol Obstet 2017; 39: 433-5. English.
6. Lee MY, Dalpiaz A, Schwamb R, et al. Clinical pathology of Bartholin's glands: a review of the literature. Curr Urol 2015; 8: 22-5.
7. Omole F, Kelsey RC, Phillips K, Cunningham K. Bartholin duct cyst and gland abscess: office management. Am Fam Physician 2019; 99: 760-6.
8. Mayeaux EJ Jr, Cooper D. Vulvar procedures: biopsy, Bartholin abscess treatment, and condyloma treatment. Obstet Gynecol Clin North Am 2013; 40: 759-772.
9. Wechter ME, Wu JM, Marzano D, et al. Management of Bartholin duct cysts and abscesses: a systematic review. Obstet Gynecol Surv 2009; 64: 395-404.
10. Speck NM, Boechat KP, Santos GM, et al. Treatment of Bartholin gland cyst with CO2 laser. Einstein (Sao Paulo) 2016; 14: 25-9.
11. Kroese JA, van der Velde M, Morssink LP, et al. Word catheter and marsupialisation in women with a cyst or abscess of the Bartholin gland (WoMan-trial): a randomised clinical trial. BJOG 2017; 124: 243-49.
12. Kafali H, Yurtseven S, Ozardali I. Aspiration and alcohol sclerotherapy: a novel method for management of Bartholin's cyst or abscess. Eur J Obstet Gynecol Reprod Biol 2004; 112: 98-101
13. Illingworth B, Stocking K, Showell M, Kirk E, Duffy J. Evaluation of treatments for Bartholin's cyst or abscess: a systematic review. BJOG 2020; 127: 671-8.
14. Krissi H, Shmuely A, Aviram A, From A, Edward R, Peled Y. Acute Bartholin's abscess: microbial spectrum, patient characteristics, clinical manifestation, and surgical outcomes. Eur J Clin Microbiol Infect Dis 2016; 35: 443-6.
15. Riche VP, Schirr-Bonnans S, Cardaillac C, et al. Hospital care pathway of women treated for Bartholin's gland abscess and budget impact analysis of outpatient management: A national hospital database analysis. J Gynecol Obstet Hum Reprod 2020; 49: 101689.
16. Cardaillac C, Dochez V, Gueudry P, et al. Surgical management of Bartholin cysts and abscesses in French university hospitals. J Gynecol Obstet Hum Reprod 2019; 48: 631-5.
17. Ozdegirmenci O, Kayikcioglu F, Haberal A. Prospective randomized study of marsupialization versus silver nitrate application in the management of bartholin gland cysts and abscesses. J Minim Invasive Gynecol 2009; 16: 149-52.
18. Mungan T, Uğur M, Yalçin H, Alan S, Sayilgan A. Treatment of Bartholin's cyst and abscess: excision versus silver nitrate insertion. Eur J Obstet Gynecol Reprod Biol 1995; 63: 61-3.
19. Cho JY, Ahn MO, Cha KS. Window operation: an alternative treatment method for Bartholin gland cysts and abscesses. Obstet Gynecol 1990; 76: 886-8.
20. Rotem R, Yahoy D, Diamant C, et al. Risk factors associated with recurrent referral to the emergency room following surgical treatment of Bartholin's gland abscess. J Obstet Gynaecol 2020; 40: 111-5.

Original Article

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How did research article publications on the COVID-19 pandemic progress in the Q1 ranked SCImage index journals in 2020?

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ABSTRACT

Aim: The aim of this paper is to survey the COVID-19 research articles in Q1 ranked high SJR index journals according to the SCImago journal rank indicator.

Material and Method: The study was carried out on the website named "https://www.scimagojr.com". The search was conducted by selecting the criteria "medicine", "pathology and forensic medicine", "all regions/countries", "journals", and the "2020" as the year. Only 50 scientific journals met these criteria. COVID-19-related and unrelated research articles published in these journals were manually scanned. Review articles, book reviews, conferences, commentaries, case reports, mini reviews, short communications, letters to the editor were not included in the study. COVID-19 related research articles were divided into groups in terms of antemortem and postmortem type of the study by reviewing the abstract of the studies and also grouped according to the country of first author and countries of all authors.

Results: A total of 3906 research articles published in 50 journals with Q1 SJR index over 0.887 were investigated. Of these 3906 research articles, 40 of them were related to COVID-19. 31 of these 40 COVID-19 related research articles were antemortem and 9 were postmortem studies. Among these 40 COVID-19 related scientific articles, the first author of publications belonged to 12 countries. United States, Australia, China, and Italy were found to be the most productive countries for published research articles on COVID-19 in selected high SJR index journals. The United States was the country with the highest number of first authors with 15 articles. China was the country with the highest number of multinational author list research articles.

Conclusion: We believe that the number and content of studies conducted in these high-quality scientific journals on COVID-19 make important contributions and understanding in the fields of disease transmission, disease prevention, course and severity of symptoms, pathophysiology, molecular characteristics, and treatment approach processes.

Keywords: COVID-19, SARS-CoV-2, publications, SCImage index

INTRODUCTION

The COVID-19 pandemic caused by SARS-CoV-2 emerged in late 2019 and negatively affected all humanity as a global health problem, infecting approximately 261 million people in total of 224 countries as of November 29, 2021, and causing the death of more than 5 million people in the World (1,2).

According to world health organization data, COVID-19 disease is asymptomatic in about 80% of cases. The remaining 20% show symptoms of respiratory system disease, and 5% of them need respiratory system support. Although COVID-19 disease primarily affects the respiratory system, extrapulmonary organs such as the heart, liver, kidneys, and nervous system can also be affected (2).

Coronaviruses are enveloped, non-segmented, positive single-stranded RNA viruses (3,4). It is reported that there is evidence that human-to-human transmission of COVID-19 occurs through respiratory particles, personal contact and fecal oral route (3). SARS-CoV-2 (COVID-19) infection causes upper respiratory tract infections and most people infected with COVID-19 recover with mild to moderate symptoms (5). However, elder people and people associated with comorbidities like cardiovascular disease, hypertension, diabetes, obesity, respiratory disease, chronic kidney, and liver disease have higher mortality rates (3-7). Diffuse alveolar damage, the histomorphologic counterpart of acute respiratory distress syndrome (ARDS) in SARS-COV-2 infected individuals, is thought to be responsible for the

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majority of deaths, followed by shock, heart damage, pulmonary embolism, thrombosis, and stroke (4,6,7). SARS-CoV-2 has a 79.6% similarity in genetic sequence with SARS-CoV, which causes severe acute respiratory syndrome (SARS), and MERS-CoV, which causes Middle East respiratory syndrome (MERS) (3,8,9).

With the rapid spread of COVID-19 cases all over the world, scientific studies have carried out quickly in the very beginning of the disease, especially in China, which is known as the country where the disease begun. Scientific studies related to COVID-19 have the priority for the rapid collection of information about the disease mechanism, pathogenesis, and the development of treatment modalities. In particular, postmortem autopsy studies are considered to be the gold standard in understanding the pathophysiology of COVID-19 disease (3,10). The aim of this paper is to investigate the COVID-19 studies in Q1 journals with SJR index higher than 0.887 in the ranking made according to the SCImago journal rank indicator.

MATERIAL AND METHOD

Since this study is a data mining study, there is no need for ethics committee approval. All procedures applied in the study were carried out in accordance with the Declaration of Helsinki and ethical criteria.

SCImago journal rank indicator is described as "a measure of journal's impact, influence, and prestige. It expresses the average number of weighted citations received in the selected year by the documents published in the journal in the three previous years".

This study was conducted on the website at "https://www.scimagojr.com". The search was made by selecting the criteria "medicine" as the subject areas of the journal, "pathology and forensic medicine" as the subject category, "all regions/countries" as the country, "journals" as the type of scientific material, and 2020 as the year. Scientific journals classified as "Q1 journals with SJR index higher than 0.887" in the ranking made according to the SCImago journal rank indicator were included in the study.

There were 50 scientific research articles that met these criteria. COVID-19-related research articles published in these high-quality journals were manually scanned. Only published research articles related to COVID-19 were investigated in this study. Review articles, book reviews, conferences, commentaries, case reports, mini reviews, short communications, letters to the editor were not included in the study. The title of the research articles in each journal was inspected manually for the presence of the terms "SARS-CoV-2" and "COVID-19". Research articles were divided into two groups, COVID-19 related and unrelated. Afterward, the COVID-19 related research articles group were divided into groups in terms of antemortem and postmortem type of the study by reviewing the abstract of the studies. In addition, COVID-19 related research articles were also reviewed according to the countries of the authors. The nation of the first author noted and the whole authors of the study were considered the criterion to be one country or multi country (multinational) type of study.

RESULTS

In this study, a total of 3906 research articles published in 50 journals with Q1 SJR index over 0.887 were reviewed in 2020. There are a total of 50 journals included in the Q1 SJR index over 0.887, and 13 of them published research articles related to COVID-19 in 2020. Of these total 3906 research articles published, 40 of them were related to COVID-19 (**Table 1**). COVID-19 related research articles were primarily composed of antemortem studies. Of these 40 COVID-19 related research articles, 31 were antemortem and 9 were postmortem studies (**Table 2**). Among these 40 scientific journals, the first author's country of COVID-19 publications belonged to a total of 12 countries namely the United States, Australia, China, Italy, and United Kingdom, Georgia, Germany, Spain, Republic of Korea, Switzerland, Brasil, Singapore when ranked from the highest number of publications to the lowest with the last 8 country same as 1 research article (**Figure 1**) (**Table 3**). Six of these 40 research articles have authors more than one country (**Table 3**). The publishing countries of scientific journals selected according to the established criteria were the United Kingdom, USA, Germany, Ireland, Netherlands, Japan, India, Switzerland, and Denmark. 21 of these 50 scientific journals selected according to the established criteria belonged to the United Kingdom, 17 of them to the USA, five to Germany, two to Ireland, one to each country of the Netherland, Japan, India, Switzerland, and Denmark.

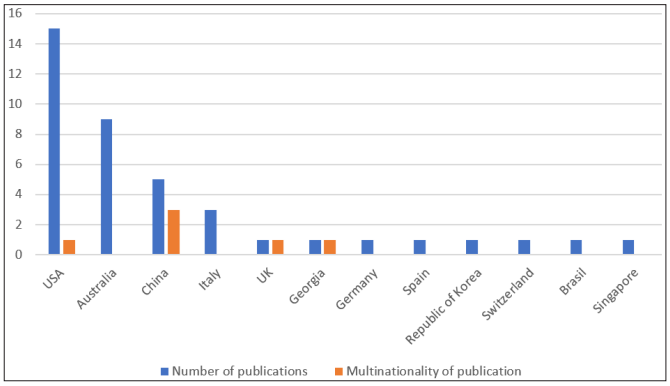

Figure 1. The country of publications and multinationality of COVID-19 studies in Q1 SJR index over 0.887 journals in 2020

Table 1. Ratio of COVID-19 related research articles in 2020 in Q1 SJR index over 0.887 journals

Research Articles	Number (%)
COVID-19 related	40 (1.02%)
Non-COVID-19 related	3866 (98.98%)
TOTAL	3906 (100)

Table 3. The country of the first authors of publications and multinationality of COVID-19 studies in selected journals in 2020

Country	Number of publications	Multinationality of publication
USA	15	1
Australia	9	0
China	5	3
Italy	3	0
UK	1	1
Georgia	1	1
Germany	1	0
Spain	1	0
Republic of Korea	1	0
Switzerland	1	0
Brasil	1	0
Singapore	1	0
TOTAL	40	6

DISCUSSION

The COVID-19 pandemic has become a global health problem and has caused the death of a large number of people all over the world. In COVID-19 disease process, humanity has not only struggled with the disease itself, but also with the secondary socioeconomic problems it has created in society. COVID-19 disease caused by SARS-CoV-2, which spreads worldwide from Wuhan, China, and caused %2 of the death of COVID-19 patients as an average mortality rate worldwide, is a member of the beta coronavirus family (1,3,11-13). It is reported that during the pandemic process, a lot of scientific researches was carried out, in particular, the molecular and biological mechanisms of COVID-19 as well as diagnosis and treatment (14-22). Analyzing the literature related to COVID-19 helps us to evaluate the pathophysiologic mechanism of the disease and understand its progression.

The ratio of the antemortem studies to the postmortem autopsy studies may also be a matter of curiosity in some aspects. There are also some combined antemortem and postmortem studies in the literature (23,24). In our study, we found that there were more COVID-19 related antemortem research studies than postmortem ones. Postmortem studies are very valuable in terms of assessing the pathogenesis of the disease caused by SARS-CoV-2 and its systemic effects on organs as a whole. In contrast, antemortem studies have provided important and valuable information about the clinical course, symptoms, therapeutic and diagnostic processes

Table 2. Q1 SJR index over 0.887 journals list and COVID-19 related research articles in 2020

Q1 SJR index over 0.887 journals	Antemortem research articles	Postmortem research articles	Total number of research articles
Annual Review of Pathology: Mechanisms of Disease	0	0	0
Cell Systems	2	0	2
Acta Neuropathologica	0	0	0
Criminology	0	0	0
Acta neuropathologica communications	0	0	0
Journal of Pathology	0	1	1
American Journal of Surgical Pathology	0	0	0
Modern Pathology	4	3	7
Neuropathology and Applied Neurobiology	0	0	0
Journal of Molecular Diagnostics	4	0	4
Journal of Quantitative Criminology	0	0	0
Justice Quarterly	0	0	0
Brain Pathology	0	0	0
Journal of Pathology: Clinical Research	0	0	0
Aging and Disease	4	0	4
Archives of Pathology and Laboratory Medicine	0	0	0
Cell and Tissue Research	0	0	0
Histopathology	2	3	5
Advances in Anatomic Pathology	0	0	0
American Journal of Pathology	3	0	3
Aggression and Violent Behavior	0	0	0
Laboratory Investigation	1	0	1
Expert Review of Molecular Diagnostics	0	0	0
Journal of Neuropathology and Experimental Neurology	0	0	0
Crime and Delinquency	0	0	0
Journal of Neurodevelopmental Disorders	0	0	0
British Journal of Criminology	0	0	0
Pathology	10	0	10
Theoretical Criminology	0	0	0
European Journal of Cell Biology	0	0	0
Cytometry. Part A : the journal of the International Society for Analytical Cytology	0	0	0
Criminal Justice and Behavior	0	0	0
BBA Clinical	0	0	0
Virchows Archiv	0	2	2
Human Pathology	0	0	0
Seminars in Diagnostic Pathology	0	0	0
Current Pathobiology Reports	0	0	0
Forensic Science International: Genetics	0	0	0
Science and Justice - Journal of the Forensic Science Society	0	0	0
Forensic Toxicology	0	0	0
Journal of Clinical Pathology	0	0	0
Journal of Pathology Informatics	1	0	1
Endocrine Pathology	0	0	0
Homicide Studies	0	0	0
International Journal of Legal Medicine	0	0	0
Pathobiology	0	0	0
International Journal of Gynecological Pathology	0	0	0
Forensic Science International	0	0	0
APMIS	0	0	0
Journal of Oral Pathology and Medicine			
TOTAL	31	9	40

of COVID-19 disease. We think that the higher number of antemortem studies is due to the fact that the centers conducting postmortem examinations are limited. In addition, in COVID-19 cases, it is necessary to apply maximum biosecurity protection methods to perform an autopsy and take postmortem samples. Due to such factors that caused delays in the process, at the very beginning of the COVID-19 pandemic, autopsy studies and, as a result, data obtained from autopsies were limited (3,7). In the later days of COVID-19 pandemic period, knowledge of protection methods and the information obtained about the disease increased, and then postmortem studies also increased in number.

The subject group we investigated in this study were those related to pathology and forensic medicine. Among the 50 scientific journals selected according to the predetermined criteria, the journal that published the most research articles related to COVID-19 was named "Pathology". The journal "Pathology" published a special issue for COVID-19 and 10 research articles were published in this special issue. Journals associated with pathology during the pandemic process have provided important information related to the mechanism of COVID-19 disease. Of the 50 scientific journals we reviewed, 4 had the word "forensic" and 4 had the word "criminology" in the name of the journal. There was no research article related to COVID-19 disease in these 8 journals in 2020. Although the lack of COVID-19-related studies in journals associated with the field of criminology was considered normal, it was interesting that there were no postmortem research studies in these high quality forensic journals.

The majority of the studies conducted on COVID-19 related research papers were of the United States in origin as the first author's country. Of these 15 United States origin studies, only one had a multinational list of authors. There are some recent published multinational studies on COVID-19 (25-27). We think that multinational studies are important, especially in terms of sharing the knowledge and experience collected about COVID-19 in different countries. There were some multinational studies It is an interesting detail that despite the fact that the SARS-CoV-2 caused COVID-19 disease originated in the Chinese city of Wuhan, the most research publications on this subject in the journals included in the criteria we have determined were the authors of the United States. China, on the other hand, was the country that had the highest number of scientific research articles with multinational authors list on this subject, with 3 in number. We think that this is primarily due to the fact that the disease caused by SARS-CoV-2 originated from the Chinese city of Wuhan, and the scientists of this country have shared the information they have obtained with scientists located internationally at the very beginning of the disease. Senel and Topal (28) investigated all the coronavirus-related literature between the year 2000-2009 and found that a total of 4810 documents were produced, and reported as 82% of them were original articles. They also stated that the most productive countries in scientific publications related to COVID-19 were United States, China, Germany, United Kingdom, and Netherlands, and also reported that almost every country contributed to the literature, except for some countries in Asia and Africa (28). In our study, we identified the United States, Australia, China, and Italy as the most productive countries for research articles on COVID-19 in selected high SJR index journals.

There are various retrospective and data mining studies evaluating the contents and results of COVID-19 related scientific studies. Zdravkovic et al (29) reported that search for the word "COVID-19" or "SARS-CoV-2" in PubMed revealed 4,670 scientific publications in about 3 months of early 2020. In this study, it was stated that a large number of scientific studies related to COVID-19 were supported by the ethics committees and the editors and were published quickly (29). However, they expressed that this process, which is progressing rapidly, raises concerns about the quality of scientific studies (29). In that study, it is stated that the first COVID-19 transmission report in asymptomatic individuals was later found to be defective (29,30). There were also two main analyses of hydroxychloroquine use and COVID-19 related cardiovascular mortality that were withdrawn because the source data could not be verified (29,31,32). In addition, country based and publication content-based studies related to COVID-19 publications are also available in the literature (2,5). A review by Ciftciler et al (5) described the scientific studies related to COVID-19 conducted in Turkey. In addition, genetic and molecular studies on COVID-19 by Tanoğlu and Esen (2) have been retrospectively investigated. Another study by Inanc et al (3) analyzed the studies of COVID-19 in rural areas of Turkey in detail. H and Patil (33) investigated Indian publications of SARS-CoV-2. In our study, COVID-19 related research studies in journals with a high SCImage index in the field of pathology and forensic medicine were investigated and reviewed.

Limitations of study

As some of these scientific journals selected according to the criteria in our study are related to certain special topics such as forensic, neuropathology, justice, and criminology, the lack of publications related to COVID-19 in these journals has an obstacle for possible comparisons among these scientific journals.

CONCLUSION

The contribution of scientific studies conducted in the process of developing treatment and understanding the pathogenesis of COVID-19 disease is the priority, and we consider that data on the number of research publications in scientific journals with a high value of the SJR index are important in this process.

While humanity is struggling with the health and socioeconomic problems caused by the COVID-19 pandemic, scientific research articles, especially high-quality publications, have been decisive in understanding the progression, mechanism, and pathophysiology of the disease and have led to the development of treatment protocols and procedures. Therapeutic studies on SARS-CoV-2 infection and newly developing mutations are continuing intensively in the world. The number and content of studies conducted in these high-quality scientific journals on this subject make important contributions to the understanding of disease transmission, disease prevention, course and severity of symptoms, pathophysiology, molecular characteristics, and treatment approach processes.

ETHICAL DECLARATIONS

Ethics Committee Approval: This current study is a data-mining study and only contain open access data. There is no need to obtain ethical committee approval.

Informed Consent: There is no need to obtain informed consent.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Worldometers (2021). COVID-19 coronavirus pandemic [Online]. Website: www.worldometers.info/coronavirus/ [Accessed 17 08 2021].
2. Tanoglu EG, Esen MF. Evaluation of studies on molecular biology and genetics related to COVID-19 with data mining. J Health Sci Med 2021; 4: 960-6.
3. Inanc IH, Bursa N, Gültepe A, Sabanoglu C. The impact of COVID-19 on rural population: A retrospective study. J Health Sci Med 2021; 4: 722-7.
4. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 2020; 77: 198-209.
5. Ciftciler R, Haznedaroglu IC, Tufan A, Oztürk MA. COVID-19 scientific publications from Turkey. Turk J Med Sci 2021; 51: 877-89.
6. Das T, Bugra A, Arslan MN, Ziyade N, Buyuk Y. Evaluation of postmortem pathological changes in the lung in SARS-CoV-2 RT-PCR positive cases. J Surg Med 2021; 5: 1113-20.
7. Satturwar S, Fowkes M, Farver C, et al. Postmortem findings associated with SARS-CoV-2: systematic review and meta-analysis. Am J Surg Pathol 2021; 45: 587-603.
8. Martines RB, Ritter JM, Matkovic E, et al. Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. Emerg Infect Dis 2020; 26: 2005-15.
9. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-3.
10. Bryce C, Grimes Z, Pujadas E, et al. Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience. Mod Pathol 2021; 34: 1456–67.
11. Alshammary AF, Al-Sulaiman AM. The journey of SARS-CoV-2 in human hosts: a review of immune responses, immunosuppression, and their consequences. Virulence 2021; 12: 1771-94.
12. Khan M, Adil SF, Alkhathlan HZ, et al. COVID-19: a global challenge with old history, epidemiology and progress so far. Molecules 2020; 26: 39.
13. Adil MT, Rahman R, Whitelaw D, et al. SARS-CoV-2 and the pandemic of COVID-19. Postgrad Med J 2021; 97: 110-6.
14. James N, Menzies M. Trends in COVID-19 prevalence and mortality: A year in review. Physica D 2021; 425: 132968.
15. Tang YW, Schmitz JE, Persing DH, Stratton CW. Laboratory diagnosis of COVID-19: current issues and challenges. J Clin Microbiol 2020; 58: e00512-20.
16. Garg A, Ghoshal U, Patel SS, et al. Evaluation of seven commercial RT-PCR kits for COVID-19 testing in pooled clinical specimens. J Med Virol 2021; 93: 2281-6.
17. Tianyu Z, Liying G. Identifying the molecular targets and mechanisms of xuebijing injection for the treatment of COVID-19 via network parmacology and molecular docking. Bioengineered 2021; 12: 2274-87.
18. de Jesus SF, Santos LI, Rodrigues Neto JF, et al. Therapeutic perceptions in antisense RNA- mediated gene regulation for COVID-19. Gene 2021; 800: 145839.
19. Rödel J, Egerer R, Suleyman A, et al. Use of the variplex™ SARS-CoV-2 RT-LAMP as a rapid molecular assay to complement RT-PCR for COVID-19 diagnosis. J Clin Virol 2020; 132: 104616.
20. Iserson KV. SARS-CoV-2 (COVID-19) vaccine development and production: an ethical way forward. Camb Q Healthc Ethics 2021; 30: 59-68.
21. Xiong D, Dai W, Gong J, et al. Rapid detection of SARS-CoV-2 with CRISPR-Cas12a. PLoS Biol 2020; 18: e3000978.
22. Anderson EJ, Campbell JD, Creech CB, et al. Warp speed for coronavirus disease 2019 (COVID-19) vaccines: why are children stuck in neutral? Clin Infect Dis 2021; 73: 336-40.
23. Santana MF, Pivoto G, Alexandre MAA, et al. Confirmed invasive pulmonary aspergillosis and COVID-19: the value of postmortem findings to support antemortem management. Rev Soc Bras Med Trop 2020; 53: e20200401.
24. Gagiannis D, Umathum VG, Bloch W, et al. Antemortem vs postmortem histopathologic and ultrastructural findings in paired transbronchial biopsy specimens and lung autopsy samples from three patients with confirmed SARS-CoV-2. Am J Clin Pathol 2021; aqab087.
25. Chew NWS, Lee GKH, Tan BYQ, et al. A multinational, multicentre study on the psychological outcomes and associated physical symptoms amongst healthcare workers during COVID-19 outbreak. Brain Behav Immun 2020; 88: 559-65.

26. Antúnez-Montes OY, Escamilla MI, Figueroa-Uribe AF, et al. COVID-19 and multisystem inflammatory syndrome in latin american children: a multinational study. Pediatr Infect Dis J 2021; 40: e1-e6.
27. Ceulemans M, Foulon V, Ngo E, et al. Mental health status of pregnant and breastfeeding women during the COVID-19 pandemic-A multinational cross-sectional study. Acta Obstet Gynecol Scand 2021; 100: 1219-29.
28. Şenel E, Topal FE. Holistic analysis of coronavirus literature: a scientometric study of the global publications relevant to SARS-CoV-2 (COVID-19), MERS-CoV (MERS) and SARS-CoV (SARS). Disaster Med Public Health Prep 2020; 1-8.
29. Zdravkovic M, Berger-Estilita J, Zdravkovic B, Berger D. Scientific quality of COVID-19 and SARS CoV-2 publications in the highest impact medical journals during the early phase of the pandemic: A case control study. PLoS One 2020; 15: e0241826. Erratum in: PLoS One 2021; 16: e0250141.
30. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Eng J Med 2020; 382: 970–1.
31. Mehra MR, Ruschitzka F, Patel AN. Retraction—hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet 2020; 395: 1820.
32. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: cardiovascular disease, drug therapy, and mortality in COVID-19. N Engl J Med 2020; 382: 2582.
33. N VR, Patil SB. Indian Publications on SARS-CoV-2: A bibliometric study of WHO COVID-19 database. Diabetes Metab Syndr 2020; 14: 1171-8

Original Article

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Effects of blood group types on risk of infection, disease severity, and mortality in COVID-19 patients

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ABSTRACT

Aim: COVID-19 is an epidemic communicable disease that has been declared as a pandemic caused by severe acute respiratory syndrome coronavirus 2. Clinical studies have demonstrated that advanced age and comorbid conditions enhance the severity of the infection. The objective of this study was to examine the of effects of blood group types on risk of infection, disease severity, and mortality in COVID-19 patients.

Material and Method: Included in this study were 1618 patients who had been diagnosed with PCR confirmed COVID-19 infection. The age, gender, blood type, disease severity, need for intensive care, and deaths of the patients were analyzed retrospectively. For the distribution of the blood types in a healthy population, statistics for the blood types of individuals in Ankara for 2020 were obtained from the Republic of Turkey Red Crescent Blood Services and used as a healthy control group for comparison with the data of the patients included in the study.

Results: Among the COVID-19 patients, blood type A was the most common type at a rate of 46.2%. This was followed by blood type O at a rate of 28.4%. The least common blood type was found to be type AB at a rate of 9%. When compared to the healthy population, blood type A was determined to be statistically significantly more common in COVID-19 infection ($p=0.07$,). In contrast, blood type O was determined to be less common when compared to the healthy population ($p<0.001$). No statistically significant differences were determined between the blood types and the risk of severe disease and mortality rate.

Conclusion: Based upon the results of the study, it can be hypothesized that blood group type O may be protective against the risk of contracting the disease and the development of severe infection, while blood group type A may be associated with an increased risk of contracting the disease. However, it was determined that there were no statistically significant associations of mortality and the development of severe disease with ABO blood types.

Keywords: Blood groups, COVID-19, SARS-CoV-2, disease severity, mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) first emerged in Wuhan Province, China, as a severe infection involving respiratory system. After that, it was declared a pandemic by the World Health Organization due to the global spread of the disease (1).

Prognosis of the disease caused by COVID-19 infection varies with age, comorbidities, and gender, although a prognostic risk factor specific to this disease has not been determined. The association between blood types and prognosis of the disease is among the risk factors in the literature that have not yet been clarified.

As is known, susceptibility to some viral infections has been linked to antigenic determinants of ABO blood types. Several previous studies have revealed an association between Hepatitis B and Norwalk virus infections and blood types (2,3). Similarly, several studies have shown that ABO blood types also are important risk factors for cardiovascular diseases and venous thromboembolism (VTE) (4,5). Risk of thrombosis has been reported to be lower in individuals with type O blood when compared to those with other blood types and, according to the most recent data, ABO blood types have been shown to modulate the risk of thrombosis via biological mechanisms (6,7). In Turkey and worldwide,

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there have been a limited number of studies conducted that have examined the association between SARS-CoV-2 and ABO blood types (8-11). Therefore, in this study, it was aimed to conduct an examination of the effects of blood types on the risk of infection, disease severity, and mortality in COVID-19 patients.

MATERIAL AND METHOD

Ethics codes were followed, the patients were told about diagnostic and treatment protocols in detail, and informed consent forms regarding the use of their medical information were signed by the patients during their hospitalization. The study was carried out with the permission of Ankara City Hospital No:1 Clinical Research Ethics Committee (Date: 21.05.2020, Decision No: 626). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was conducted at the department of Internal Diseases between March 2020 and January 2021. Patients with SARS-CoV-2 RNA polymerase chain reaction (PCR)-confirmed COVID-19 infection were included in the study. Patients with no data about their blood type on the system and those with no reachable data for their blood type were excluded from the study. For the PCR tests of the patients, nasopharyngeal swab samples were used. Patient medical data were examined retrospectively. The patient data, including age, gender, comorbidities, and need for intensive care, were obtained from medical records. According to the severity of the disease, we classified the patients into two groups as non-severe and severe patients (**Figure**) (12,13). For distribution of the blood types in a healthy population, statistics for blood types in Ankara for 2020 were obtained from the Republic of Turkey Red Crescent Blood Services and used as a healthy control group for comparison with patient data. A 10000-patient sample from data about blood types of the whole population in Ankara was obtained. These data were used as a healthy control group for comparison with the patient data.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows 25.0 (IBM Corp., Armonk, NY, USA). For evaluation of the study data, descriptive statistical methods [frequency, percentage, median, interquartile range (IQR)] were used, as well as the chi-square ($\chi 2$) test for comparison of the qualitative data. Conformity to normal distribution of the data was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For comparison of the data exhibiting normal distribution, the Mann-Whitney U test was used. Risk analysis was used to determine the risk rates. Statistical significance was considered as α=0,05.

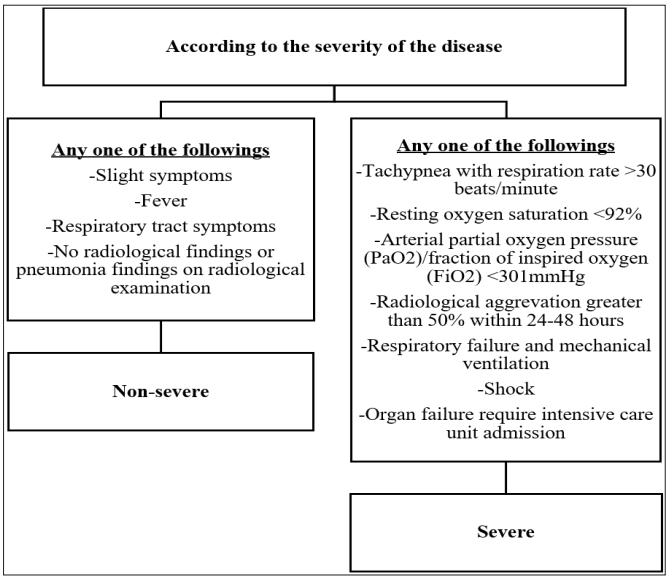

Figure. Flowchart of COVID-19 disease stage as non-severe and severe

RESULTS

A total of 1618 patients with a positive COVID-19 PCR test were included in the study population. The clinical and demographic findings of the patients, as well as their distribution by blood type and disease severity are represented in **Table 1** and **Table 2**. The median age of the patients was determined to be 63 years. For the distribution by gender, 57.8% of the patients were male. Among the COVID-19 patients, type A was the most common blood type, at a rate of 46.2%. This was followed by type O at a rate of 28.4%. The least common was type AB, at a rate of 9%.

When compared to the healthy population, type A was determined to be statistically significantly more common in COVID-19 infection (46.2% versus 42.6%; p=0.007, OR: 1.157). In contrast, type O was determined to be less common when compared to the healthy population (28.4% versus 33.1%; p < 0.001, OR: 0.802).

The distribution of COVID-19 patients by disease severity and mortality rates are given in **Table 3** and **Table 4**. No statistically significant difference was determined between the blood types with regards to the risk of severe disease (p=0.990) and, among the COVID-19 patients, no statistically significant difference was determined between the blood types with regards to the mortality rates (p=0.907).

Table 1. Demographic evaluation of groups with mild and severe diseases

	All Patients	ICU Admission (Severe Disease)		p value
	(n=1618)	Severe (n=814)	Non-severe (n=804)	
Gender Male	936 (57.8%)	478 (58.7%)	458 (57.0%)	0.474[a]
Age (year)	63.00 (27.00)	72.00 (20.00)	52.00 (27.00)	0.000[b]

a: Chi-square test (n/%), b: Mann-Whitney U test (median/IQR)

Table 2. Comparison of the Blood Groups of the Healthy Controls and COVID-19 Patients

Blood Type	Group		P-value*		
	COVID-19 (n=1618)	Healthy Controls (n=10000)			
O	459 (28.4%)	3305 (33.1%)			
A	748 (46.2%)	4264 (42.6%)	0.002		
B	265 (16.4%)	1629 (16.3%)			
AB	146 (9.0%)	802 (8.0%)			
Blood Type	**COVID-19 (n=1618)**	**Healthy Controls (n=10000)**	**P-value***	**OR**	**95% CI**
O	459 (28.4%)	3305 (33.1%)	0.000	0.802	0.714–0.901
A	748 (46.2%)	4264 (42.6%)	0.007	1.157	1.041–1.285
B	265 (16.4%)	1629 (16.3%)	0.929	1.006	0.873–1.160
AB	146 (9.0%)	802 (8.0%)	0.171	1.138	0.946–1.368

*: Chi-square test (n / %)

Table 3. Disease Severity in COVID-19 Patients by Blood Group

Blood Type	ICU admission (Severe Disease)		P-value*		
	Severe (n=814)	Non-severe (n=804)			
O	233 (28.6%)	226 (28.1%)			
A	373 (45.8%)	375 (46.6%)	0.990		
B	134 (16.5%)	131 (16.3%)			
AB	74 (9.1%)	72 (9.0%)			
Blood Type	**ICU Admission (Severe Disease)**		**P-value***	**OR**	**95% CI**
	Severe (n=814)	**Non-severe (n=804)**			
O	233 (28.6%)	226 (28.1%)	0.818	0.975	0.785–1.210
A	373 (45.8%)	375 (46.6%)	0.957	1.005	0.827–1.222
B	134 (16.5%)	131 (16.3%)	0.927	0.988	0.759–1.285
AB	74 (9.1%)	72 (9.0%)	0.924	0.984	0.700–1.382

*: Chi-square test (n/%)

Table 4. Status of the Life of COVID-19 Patients by Blood Group

Blood Type	Survivor/Non-survivor		P-value*		
	Survivor (n=1211)	Non-survivor (n=407)			
O	338 (27.9%)	121 (29.7%)			
A	562 (46.4%)	186 (45.7%)	0.907		
B	200 (16.5%)	65 (16.0%)			
AB	111 (9.2%)	35 (8.6%)			
Blood Type	**Survivor/Non-survivor**		**P-value***	**OR**	**95% CI**
	Survivor (n=1211)	**Non-survivor (n=407)**			
O	338 (27.9%)	121 (29.7%)	0.481	1.093	0.854–1.399
A	562 (46.4%)	186 (45.7%)	0.804	0.972	0.776–1.218
B	200 (16.5%)	65 (16.0%)	0.797	0.961	0.708–1.304
AB	111 (9.2%)	35 (8.6%)	0.730	0.932	0.626–1.388

*: Chi-square test (n/%)

DISCUSSION

In this study, it was determined that, among the COVID-19 patients, the most common blood type was A, while the least common was type AB. Type A was determined to be statistically significantly more common in the COVID-19 group when compared to the healthy control, whereas type O was determined to be less common. While the types differed between the COVID-19 and healthy control groups, no association with disease severity or mortality was found.

The relationship between ABO blood groups and COVID-19 has been evaluated in previous studies and meta-analyses (14-18). In a meta-analysis published by Pendu et al., a general consensus emerged that O blood type appears to be associated with a lower risk of COVID-19 and non-O blood types appear to be harmful in 34 current studies. They supported this with two opinion. Natural anti-A and anti-B antibodies may be partially protective against SARS-CoV-2, which carries blood group antigens originating from non-O patients. In addition, O patients are less prone to thrombosis and vascular dysfunction than non-O patients and may be less at risk in the case of severe lung dysfunction (15). Parallel to this, in our study, it was also thought that type A blood may be associated with an increased risk for COVID-19, and the same pathophysiological hypothesis may play a role in this effect.

A meta-analysis of 21 studies published by Franchini et al was found low/very low evidence that patients with O blood were less susceptible to SARS-CoV-2 infection compared to the non-O blood type. No evidence was found to indicate the effect of type O blood on disease severity in SARS-CoV-2 infection (14). In a study from Turkey conducted by Goker et al. (9), in which the effects of blood types on COVID-19 were examined, it was reported that the risk of disease may be increased in individuals with type A. In the current study, it was determined that the risk of disease was significantly increased in individuals with type A, but it was not significant with regards to mortality or the need for intensive care. In the current study, type O, however, was determined to be protective against contracting the disease. Nevertheless, the number of patients with type O was higher in the non-severe and survivor groups, although this was not statistically significant. The results of these studies support our study. In another study conducted in Turkey, Aktimur et al. found that A blood type was associated with a higher risk for COVID-19 than other blood types. Again, in the same study, it was stated that patients with A blood type had a longer intensive care unit stay, and they might have a higher risk in terms of disease severity (10). Unlike our study, a relationship was found between disease severity, intensive care hospitalization and blood group type. This difference may be due to the fact that comorbid conditions were not evaluated together with blood group. In parallel with this study, in a study conducted by Ray et al. in which 225 COVID-19 patients were included, type O was reported to be associated with less severe disease and lower mortality risk (19). COVID-19 infection is known to be associated with hipercoagulability subsequently the microtrombi that spread through pulmonary vascular structure leads to acute respiratory distress syndrome (ARDS), which is one of the most severe complications of the disease (20-22). The lower risk of severe disease in individuals who have type O blood may be explained by the lower risk of thrombosis in patients with type O blood. Blood type antigens may act as a receptor or trap for communicable organisms and may influence susceptibility to the disease in various ways, including regulating the immune response as ABO antibodies (23). In in vitro trials, it was shown that the interaction between the SARS-CoV-1 spike protein and the ACE-2 receptor may be alleviated via anti-A antibodies (24). In a population-based prospective cohort study reported from Spain, a higher incidence of complications was found in other blood groups and especially in type B blood compared to type O blood when patients were followed up for complications of COVID-19 (18). In a study conducted by Guillon et al., in which 265 COVID-19 patients were included, it was determined that the incidence of type O blood was lower among the patients who required longer hospitalization and the incidence of type A blood was higher in patients with severe COVID-19 infection when compared to the normal population (24). In our study and current literature data, it is seen that type O blood may be protective for COVID-19, but no clear data on disease severity and mortality can be obtained.

In a study conducted during the SARS epidemic in Hong Kong, the incidence of SARS-CoV-1 was found to be lower in patients with type O when compared to those with the other blood types (25). In addition, individuals with type O blood have been known to have a a lower risk of thrombosis and cardiovascular diseases due to varying glycosyltransferase activity, and increased clearance of von Willebrand Factor (vWF) and reduced circulating FVIII levels due to vWF. The lower rates of thrombosis and endothelial dysfunction may be based upon this argument (26). Further studies are needed in order to shed light on the importance of vWF-FVIII levels and endothelial cells in coagulopathy and pulmonary microvascular occlusion, which are induced by COVID-19 infection. Coagulopathy and endothelial injury in COVID-19 patients leads to a predisposition to cardiovascular events, especially in the case of underlying diabetes mellitus and hypertension. Previous studies have reported that individuals with type A blood have an increased risk of developing hypertension as a result of impaired blood flow in the vascular bed, through increasing adhesion and inflammation in the epithelial cells, which is caused when P-selectin and intracellular cell adhesion molecule 1 (ICAM1) are prevented from enzymatic clearance in the vascular wall by antigen A. Therefore, hypertensive patients with type A blood are at higher risk for severe COVID-19 infection (27,28). Due to hypercoagulability, anticoagulation is of vital importance, particularly in the treatment and follow-up of patients with lung involvement and potential microthrombi, and subsequent manifestations of ARDS may be prevented with appropriate medical treatment. The current study was important with regards to the possibility of an evaluation of the effects of ABO blood types on infectivity, severe infection, and mortality in a Turkish population and the fact that it was conducted with a large sample.

The retrospective design of this study was, however, its major limitation. Moreover, the most important limitations included the failure to determine the comorbid conditions that were effective in the disease severity and mortality, and the inability to examine the severity–mortality association. This limitation may have been related to the failure to determine an association between the blood types and the severity–mortality.

CONCLUSION

It can be hypothesized that the type O blood may be protective against contracting COVID-19 and the development of severe infection, while type A blood, however, may be associated with an increased risk of contracting the disease. However, no statistically significant association of mortality and the development of severe disease with ABO blood types was determined. Further studies are needed in order to shed light on the association between the blood types and COVID-19 infection.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Research Ethics Committee (Date: 21.05.2020, Decision No: 626).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. http: //www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Accessed on February 12, 2020).
2. Lindesmith L, Moe C, Marionneau S, et al. Human susceptibility and resistance to Norwalk virus infection. Nat Med 2003; 9: 548-53.
3. Jing W, Zhao S, Liu J, Liu M. ABO blood groups and hepatitis B virus infection: a systematic review and meta-analysis. BMJ Open 2020; 10: e034114.
4. Franchini M, Favaloro EJ, Targher G, Lippi G. ABO blood group, hypercoagulability, and cardiovascular and cancer risk. Crit Rev Clin Lab Sci 2012; 49: 137-49.
5. Ibrahim-Kosta M, Bailly P, Silvy M, et al. ABO blood group, glycosyltransferase activity and risk of venous thromboembolism. Thromb Res 2020; 193: 31-5.
6. Bowen DJ. An influence of ABO blood group on the rate of proteolysis of von Willebrand factor by ADAMTS13. J Thromb Haemost 2003; 1: 33-40.
7. Dunne E, Qi QM, Shaqfeh ES, et al. Blood group alters platelet binding kinetics to von Willebrand factor and consequently platelet function. Blood 2019; 133: 1371-7.
8. Latz CA, DeCarlo C, Boitano L, et al. Blood type and outcomes in patients with COVID-19. Ann Hematol 2020; 99: 2113-8.
9. Göker H, Aladağ Karakulak E, Demiroğlu H, et al. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. Turk J Med Sci 2020; 50: 679-83.
10. Aktimur SH, Sen A, Yazicioglu B, Gunes AK, Genc S. The assessment of the relationship between ABO blood groups and Covid-19 infection. UHOD - Int J Hematol Oncol 2020; 30: 121-5.
11. Zietz M, Zucker J, Tatonetti NP. Associations between blood type and COVID-19 infection, intubation, and death. Nat Commun 2020; 11: 5761.
12. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance, https: //apps.who.int/iris/handle/10665/330854 (Accessed on January 25, 2020).
13. Ding X, Yu Y, Lu B, et al. Dynamic profile and clinical implications of hematological parameters in hospitalized patients with coronavirus disease 2019. Clin Chem Lab Med 2020; 58: 1365-71
14. Franchini M, Cruciani M, Mengoli C, et al. ABO blood group and COVID-19: an updated systematic literature review and meta-analysis. Blood Transfus 2021; 19: 317-26.
15. Pendu JL, Breiman A, Rocher J, Dion M, Ruvoën-Clouet N. ABO blood types and COVID-19: spurious, anecdotal, or truly important relationships? a reasoned review of available data. Viruses 2021; 13: 160.
16. Wu BB, Gu DZ, Yu JN, Yang J, Shen WQ. Association between ABO blood groups and COVID-19 infection, severity and demise: A systematic review and meta-analysis. Infect Genet Evol 2020; 84: 104485.
17. Liu N, Zhang T, Ma L, et al. The impact of ABO blood group on COVID-19 infection risk and mortality: A systematic review and meta-analysis. Blood Rev 2021; 48: 100785.
18. Domènech-Montoliu S, Puig-Barberà J, Pac-Sa MR, et al. ABO Blood Groups and the Incidence of Complications in COVID-19 Patients: A Population-Based Prospective Cohort Study. Int J Environ Res Public Health 2021; 18: 10039.
19. Ray JG, Schull MJ, Vermeulen MJ, Park AL. Association between ABO and Rh blood groups and SARS-CoV-2 infection or severe COVID-19 illness: a population-based cohort study. Ann Intern Med 2021; 174: 308-15.
20. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844-7.
21. Fogarty H, Townsend L, Ni Cheallaigh C, et al. More on COVID-19 coagulopathy in Caucasian patients. Br J Haematol 2020; 189: 1060-1.
22. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol 2020; 2: e437-e45.
23. Cooling L. Blood groups in infection and host susceptibility. Clin Microbiol Rev 2015; 28: 801-70.
24. Guillon P, Clément M, Sébille V, et al. Inhibition of the interaction between the SARS-CoV spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology 2008; 18: 1085-93.
25. Cheng Y, Cheng G, Chui CH, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA 2005; 293: 1450-1.
26. O'Sullivan JM, Ward S, Fogarty H, O'Donnell JS. More on 'Association between ABO blood groups and risk of SARS-CoV-2 pneumonia'. Br J Haematol 2020; 190: 27-8.
27. Dai X. ABO blood group predisposes to COVID-19 severity and cardiovascular disease. Eur J Prev Cardiol 2020; 27: 1436-7.
28. Wu O, Bayoumi N, Vickers MA, Clark P. ABO(H) blood groups and vascular disease: a systematic review and meta-analysis. J Thromb Haemost 2008; 6: 62-9.

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Comparison of labral repair and biceps tenodesis concomitant with arthroscopic rotator cuff repair in patients between the age of 40 and 60

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ABSTRACT

Aim: Superior labrum anterior to posterior (SLAP) lesions are frequently accompanied by rotator cuff tear (RCT). The optimal treatment for type 2 and 4 SLAP lesions with RCT were not established. We aimed to compare the clinical results of SLAP repair and biceps tenodesis (BT) concomitant with arthroscopic rotator cuff repair (ARCR) in patients between 40 and 60 years old.

Material and Method: Forthy three patients (16 male, 27 females) who received ARCR concomitant with SLAP repair or BT for full-thickness rotator cuff tear were evaluated retrospectively. The patients were divided into the two groups based on treatment methods (SLAP repair, Group 1, 20 patients), (BT, Group 2, 23 patients). American Shoulder and Elbow Surgeons (ASES) score, University of California Los Angeles (UCLA) shoulder score, visual analogue scale scores (VASs), and range of motion (ROM) values were used as outcome tools.

Results: The mean age of the patients was 48.8±5.03 years. There was no difference in preoperative shoulder and pain scores ($P<0.05$). Postoperative 12th month and last follow-up ASES and UCLA scores and ROM measures were significantly higher in Group 2, but the minimally clinical important difference (MCID) was not reached in any of the shoulder scores.

Conclusion: In the patients between 40 and 60 years old, BT is associated with higher shoulder scores and ROM values than SLAP repair when performed with RCR, but the difference was clinically insignificant. We concluded that both BT and SLAP repair is suitable options with concomitant RCR.

Keywords: SLAP repair, biceps tenodesis, middle age, rotator cuff repair

INTRODUCTION

Rotator cuff tear (RCT) is one of the most common cause of shoulder pain and disability in the adult population (1). Arthroscopic repair is the treatment of choice when conservative methods fail (2). The long head of the biceps tendon (LHBT) pathologies are frequently accompanied by RCTs (3). Biceps tenotomy provides earlier relief of pain with similar satisfaction rates with biceps tenodesis (BT) (4-6), however, it may cause bicipital tenderness, cramps, and loss of supination strength and deformity. Therefore tenotomy is mainly served for elderly patients (7-9). For more demanding younger patients with type 2 or 4 superior labrum anterior to posterior (SLAP) lesions, BT or SLAP repair is widely used (10).

SLAP repair preserves normal shoulder kinematics (11), but it is related to high rates of failure and stiffness (10); therefore, the popularity of SLAP repair among shoulder surgeons decreased (12). BT is another reliable option for the management of concomitant LHBT pathologies with RCT. BT preserves normal tension of the LHBT with restoring biceps function, but complications such as anterior shoulder pain, failure, and relatively long rehabilitation period are major disadvantages of BT.

There is no consensus for the management of LHBT pathologies with RCT in the middle-aged population. Most of the recent studies favour tenotomy or BT for concomitant SLAP lesions with RCT (9, 13). However, Lim et al. compared (14) the outcomes of BT and SLAP repair with concomitant rotator cuff repair (RCR), and they reported similar functional results and complication rates. There is no guideline for the management of

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concomitant superior labrum anterior to posterior (SLAP) lesions with RCT in middle age patients (10). Therefore, the purpose of the present study was to compare clinical and functional outcomes and complication rates of labral repair and biceps tenotomy concomitant with arthroscopic rotator cuff repair (ARCR) in patients between 40 and 60 years old.

MATERIAL AND METHOD

Patients, Inclusion and Exclusion Criteria

After obtaining Institutional Ethics Review Board approval (Date: 11.02.2021, Decision No: 2021-03/14), the prospectively collected data from single-center evaluated retrospectively. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The patients who received ARCR with type 2 or 4 SLAP tears between January 2014 and January 2019 were included in the study. The inclusion criteria were (1) being between 40-60 years old at the time of surgery, (2) received transosseous equivalent ARCR because of full-thickness RCT, (3) symptomatic (+ O Brien's test) type 2 or 4 SLAP lesion confirmed by magnetic resonance imaging (MRI) preoperatively and intraoperatively, (4) received SLAP repair or BT, (5) with minimum 24 months follow up period,

The exclusion criteria were (1) partially thickness RCT, (2) receiving tenotomy, (3) other labral lesions than type 2 or 4 SLAP, (4) Grade 3 or 4 fatty degeneration according to Goutallier classification (15), (5) isolated subscapularis tear, (6) acute traumatic rotator cuff tear or SLAP injury (7) history of previous shoulder surgery or fracture from the affected side, (8) osteoarthritis in the affected shoulder, (9) preoperative frozen shoulder, (10) history of intra-articular corticosteroid injection three months before surgery, (11) incomplete medical records or (12) lost to follow-up.

After inclusion and exclusion criteria were applied, a total of 43 patients were included. The patients who received labral repair were called Group 1 (n=20), and the patients who received BT were called Group 2 (n=23).

Demographic data including age, sex, etiology, body mass index (BMI) were obtained from the patient files. Tear size was classified according to DeOrio and Cofield classification (16) based on arthroscopic examination. The number of involved tendons and the type of SLAP lesions were recorded according to arthroscopic findings as well.

Surgical Technique

All patients were operated on by two surgeons. The first surgeon performed BT, and the second performed the labral repair. The operations were performed under general anesthesia combining with interscalane block in the lateral decubitus position with longitudinal traction with 4 kilograms. A standard posterior portal was used to examine the glenohumeral joint, and then the anterior portal was established. The LHBT was examined with a probe, and the SLAP lesion was confirmed.

For the patients in Group 1, an anterosuperior portal was created, a cannula was placed, and the superior glenoid was prepared with a shaver. One or two Smith & Nephew (London, UK) TWINFIX® double-loaded suture anchor was inserted into the footprint, and the suture limbs were passed anterior and posterior to biceps anchor and tied respectively (**Figure 1**).

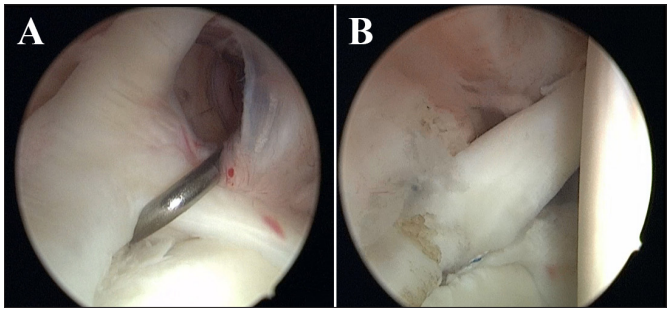

Figure 1 (a) Arthroscopic view of the SLAP 2 lesion from the posterior portal, (b) The view of LHBT-labrum complex after the repair was carried out.

For the patients in Group 2, free sutures were passed from the proximal portion of the LHBT, and the tendon was tenotomized just proximal to the sutures. Then, the sutures were loaded to the FOOTPRINT PK® suture anchor, and the anchor was inserted into the bicipital groove from the anterolateral portal without tension (**Figure 2**).

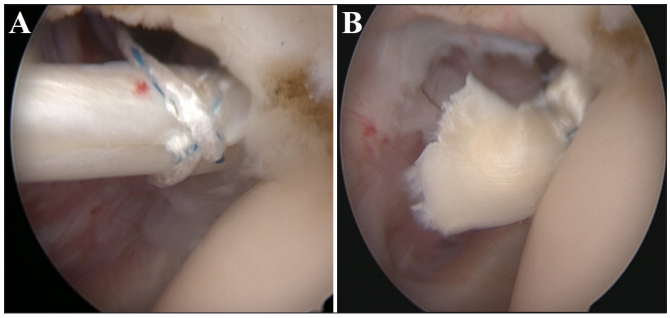

Figure 2. (a) Preparetion of the LGBT for tenodesis, **(b)** Biceps tenodesis to the bicipital groove

Then, all rotator cuff repairs were performed using transosseous equivalent technique as previously described. (17). Subacromial decompression, bursectomy, and acromioplasty were performed before repair. The footprint was debrided and prepared with a shaver. According to the tear size, one or two Smith & Nephew (London, UK) TWINFIX® double-loaded suture anchor was inserted just lateral to the articular cartilage. A lateral FOOTPRINT PK® suture anchor was placed 1 cm lateral to the footprint to compress the rotator cuff.

Postoperative Rehabilitation

The shoulder was protected at the neutral position with a shoulder sling for four weeks. Passive mobilization and pendulum exercises were started immediately. After the first four weeks, progressive active mobilization was initiated. Strengthening exercises were contraindicated for postoperative three months. The rehabilitation program was supervised and guided by an experienced physiotherapist.

Outcome Assessment

The American Shoulder and Elbow Surgeons (ASES) score (18), University of California Los Angeles (UCLA) shoulder score (19), and Visual Analogue Scale (VAS) score were used for clinical and functional assessment. Shoulder range of motion (ROM) was measured by a universal goniometer. The complications and reoperations were recorded. Shoulder stiffness was also evaluated as described previously(20). Pseudoparalysis is defined as the restriction of active shoulder abduction to 90° without limitation in passive motions (18). All assessments were completed preoperative, at postoperative 12th month, and at the last follow-up. The complications and reoperations were recorded as well. The patients who had persistent pain and limitation of motion despite physiotherapy for three months were sent to MRI, and re-tears were recorded.

Statistical Analysis

The mean, median, minimum, maximum, and standard deviation (SD) values were used to describe data. Shapiro-Wilk normality test was used to analyse the distribution of data. Independent samples t- test and Mann Whitney U tests were used in the comparison of quantitative independent data. Pre- to postoperative changes were evaluated using paired samples t-test and Wilcoxon-signed rank test. Chi-square or test was used in the comparison of qualitative data. A P-value < 0.05 was considered statistically significant. All statistical analysis was performed using IBM SPSS for Windows, version 22 (IBM Corp., Armonk, NY).

RESULTS

The study included 43 patients. The mean age of the patients was 48.8±5.03 (Range 40-59). Patients were followed mean 51.09±16.37 months (Range 24-80). Demographic and intraoperative variables of the patients were presented in **Table 1.** There was a significant difference between preoperative and postoperative 12th month ASES and UCLA scores and all the ROM values in both groups (p<0.001) and also, ASES and UCLA scores at the last follow up were higher than the postoperative 12th-month scores in both groups (p<0.01). Comparison of preoperative and postoperative shoulder scores and ROM measures between the two groups was presented in **Table 2.** In 5 patients, shoulder stiffness was observed during the follow-up period (Group 1 3/20, Group 2 2/23, p=0.520). Two patients in each group have pseudoparalysis (p=0.883). Symptomatic re-rupture was detected in the two patients in each group. One of them refused to receive another surgery in group 1, and the remaining three patients were received repair and tenotomy. There was no difference between the groups in terms of re-rupture rates (p=0.883). Three patients in each group reoperated during the follow-up period (p=0.853), etiologies were as follows, 1 re-rupture, 1 stiffness, and 1 anterior shoulder pain in group 1; 2 re-rupture and 1 anterior shoulder pain in group 2. Popeye deformity was observed in one patient from each group which was statistically not significant (Group1 5% vs. Group 2 4.34%, p=0.72).

Table 1. Demographic details and intraoperative findings of the patients

Variables	Group 1 (n=20) (Mean±SD) / n (%)	Group 2 (n=23) (Mean±SD) / n (%)	P Value
Age (Years)	48.6±6.05	49.13±4.07	0.678
Sex			0.780
Male	7 (35%)	9 (39.1%)	
Female	13 (56%)	16 (60.9%)	
Effected side			0.780
Dominant	13 (65%)	14 (60.9%)	
Nondominant	7 (35%)	9 (39.1%)	
Follow up (Months)	53.35± 15.43	49.13±17.24	0.386
BMI (kg/m2)	28.55±5.83	27.47±4.20	0.788
Etiology			0.919
Acute	1 (5%)	1 (4.3%)	
Chronic	19 (95%)	22 (95.7%)	
Tear Size			0.586
Small	7 (35%)	9 (39.1%)	
Medium	11 (55%)	11 (47.8%)	
Large	1 (5%)	3 (13.0%)	
Massive	1 (5%)	0 (0%)	
Number of involved tendons	1.55±0.68	1.30±0.55	0.191
SLAP lesion			0.756
Type 2	18 (90%)	20 (87%)	
Type 4	2 (10%)	3 (13%)	

DISCUSSION

The main finding of the study was, the patients who received ARCR with SLAP repair or BT benefit from surgery; however, the patients who received BT have higher ASES and UCLA shoulder scores postoperatively. On the other hand, internal and external rotation capacity were higher in patients who received BT at postoperative 12th month and the last follow-up. On the other hand, complication and reoperation rates were similar between the two groups.

Table 2. Comparison of clinical scores and ROM values between the two groups

Variables	Preoperative			Postoperative 12th month			Last follow-up			P Value† (Pre-Postop 12th month dif.)	P Value† (Postop 12th month-Last FU dif.)
	Group 1 (n=20) (Mean±SD)	Group 2 (n=23) (Mean±SD)	P value*	Group 1 (n=20) (Mean±SD)	Group 2 (n=23) (Mean±SD)	P value*	Group 1 (n=20) (Mean±SD)	Group 2 (n=23) (Mean±SD)	P value*		
ASES score	40.40±5.64	42.78±4.70	0.093	83.30±5.66	87.39±2.58	0.015	87.20±5.66	89.56±1.90	0.020	<0.001	<0.001
UCLA shoulder score	18.00±2.15	16.69±2.28	0.065	26.80±1.19	29.13±1.79	<0.001	29.45±2.08	32.60±1.40	<0.001	<0.001	<0.001
VAS pain score	5.50 ±1.35	5.30 ±1.10	0.659	2.20 ±0.83	2.08 ±0.79	0.726	1.80 ±0.83	1.43 ±0.58	0.128	<0.001	0.004
FF (°)	142.75±6.75	137.17±9.63	0.080	162.25±4.99	165.21±6.11	0.054	169.00±3.83	172.82±3.93	0.03	<0.001	<0.001
ABD (°)	132.50±8.95	128.47±8.03	0.103	154.00±6.40	155.65±6.27	0.424	160.75±6.34	165.43±4.24	0.016	<0.001	<0.001
ER (°)	57.20±3.27	53.56±7.31	0.560	77.40±2.25	81.34±2.72	<0.001	83.20±1.85	87.21±2.06	<0.001	<0.001	<0.001
IR (°)	49.85±3.42	47.95±3.98	0.104	72.10±2.55	74.13±2.37	0.050	76.60±2.30	79.30±3.62	0.010	<0.001	<0.001

ASES: American Shoulder and Elbow Surgeons, UCLA: University of California Los Angeles, VAS: Visual Analogue Scale FF: Forward flexion, ABD: Abduction, ER: External rotation, IR: Internal rotation, *: Mann Whitney U test, †: Paired samples t-test, dif: Difference)

In their randomised controlled study, Franceschi et al. (9) compared to repair and biceps tenotomy in RCT with SLAP 2 lesion in patients over 50 years old, and they reported that the tenotomy group has a higher UCLA shoulder score. Also, Kim et al. (13) compared BT and labral repair concomitant with large to massive RCTs, and they reported that BT is associated with higher ASES and Simple Shoulder Test scores and ROM. Forsythe et al. (21) analysed the outcomes of the simultaneous rotator cuff and SLAP repair and compared them with isolated RCR, and they reported similar postoperative functional scores and ROM capacities, although the RCR+SLAP repair group had lower preoperative shoulder scores and ROM capacities than isolated RCR. In a recent study, Lim et al. compared SLAP repair and BT concomitant with RCR in patients over 45 years old, and they reported similar Constant, ASES, and VAS scores and ROM capacities in both groups. In contrast to Lim et al. (14), we found statistically significant difference in terms of ASES and UCLA shoulder scores and ROM measures at the postoperative 12th month and last follow-up. Altough the inter-group differences were statistically significant, minimally clinical important difference (MCID) (22) was not detected neither in ASES nor UCLA shoulder scores. However, MCID values were reached in the both groups in terms of pre-postoperative differences.

Limitation of shoulder motion is a major concern after labral repair (23). Franceschi et al. (9) reported higher ROM in patients who received tenotomy and RCR compared to the simultaneous rotator cuff and SLAP repair. In another study (14), authors compared BT and SLAP repair concomitant with ARCR, and they reported similar ROM values. In their prospective study, Kanatli et al. (24) compared the clinical results of patients over the age of 45 who received repair for SLAP 2 lesion with or without RCR, and they reported similar overall UCLA scores and ROM values at an average 2.5 years follow-up. Based on their systematic review, the authors concluded that surgeons should be cautious about repairing SLAP lesions, and they suggest performing BT or tenotomy concomitant with RCR. According to our findings, patients who received BT had higher internal and external rotation capacity at the postoperative 12th month and at the last follow-up, but those difference did not cause a clinically significant difference. The rate of postoperative stiffness was also similar between the two groups.

Popeye deformity may cause dissatisfaction apart from functional outcomes (25). Although Popeye deformity is mainly associated with biceps tenotomy, it may develop after BT as well (26). Oh et al. (5) reported similar Popeye sign rates between BT and biceps tenotomy with concomitant RCTs. We did not observe any Popeye sign in the BT group; however, one of the theoretical advantage of SLAP repair over BT may be preserving normal anatomy of the LGHT-labrum complex with a lower risk of Popeye sign which may be a concern in younger male patients.

The strengths of the study were as follows. In contrast to many similar studies (14, 24, 27), we analysed the narrow age group to increase the homogeneity of the study population and included the patients between 40-60 years old. We believe that the management of SLAP lesions in the older population should be analysed separately because healing capacity may be lower, and analysing middle age and geriatric population together may cause bias. We performed standardised transosseous equivalent double-row repair for all patients; therefore, confounding factors that may affect outcomes were minimum in this study, also baseline characteristics and preoperative measures were similar between the two groups.

The study has some limitations. First, the retrospective design of the study increases the risk of selection bias. We did not obtain MRI postoperatively from asymptomatic patients; therefore, we may miss some of the asymptomatic re-tears. Second, the study population

is relatively low. Third, two surgeons performed the operations, the surgical ability of the surgeons may influence the outcomes; however, both surgeons were trained in arthroscopic shoulder surgery. Also follow-up period was relatively short to observe long-term complications such as cuff tear arthropathy. Lastly, we did not measure the quality of life scores which may be more representative of the effect of disease on the general health status of the patients.

CONCLUSION

The patients who received biceps tenodesis and labral repair for SLAP 2 and 4 lesions concomitant with rotator cuff repair significantly improved clinical scores and shoulder ROM measures. We found that biceps tenodesis is associated with better ROM but similar clinical results with SLAP repair. Therefore, we concluded that both BT and SLAP repair is suitable options with concomitant RCR in middle-aged patients. New studies are needed to create evidence-based treatment algorithms for SLAP lesions with RCT.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Acıbadem Unviersity Ethics Committee (Date: 11.02.2021, Decision No: 2021-03/14).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Minagawa H, Yamamoto N, Abe H, et al. Prevalence of symptomatic and asymptomatic rotator cuff tears in the general population: From mass-screening in one village. J Orthop 2013; 10: 8-12.
2. Plachel F, Siegert P, Rüttershoff K, et al. Long-term results of arthroscopic rotator cuff repair: a follow-up study comparing single-row versus double-row fixation techniques. Am J Sports Med 2020; 48: 1568-74.
3. Hawi N, Liodakis E, Garving C, Habermeyer P, Tauber M. Pulley lesions in rotator cuff tears: prevalence, etiology, and concomitant pathologies. Arch Orthop Trauma Surg 2017; 137: 1097-105.
4. De Carli A, Vadalà A, Zanzotto E, et. al. Reparable rotator cuff tears with concomitant long-head biceps lesions: tenotomy or tenotomy/tenodesis? Knee Surg Sports Traumatol Arthrosc 2012; 20: 2553-8.
5. Oh JH, Lee YH, Kim SH, et. al. Comparison of treatments for superior labrum-biceps complex lesions with concomitant rotator cuff repair: a prospective, randomized, comparative analysis of debridement, biceps tenotomy, and biceps tenodesis. Arthroscopy 2016; 32: 958-67.
6. Belay ES, Wittstein JR, Garrigues GE, et. al. Biceps tenotomy has earlier pain relief compared to biceps tenodesis: a randomized prospective study. Knee Surg Sports Traumatol Arthrosc 2019; 27: 4032-37.
7. MacDonald P, Verhulst F, McRae S, et. al. Biceps tenodesis versus tenotomy in the treatment of lesions of the long head of the biceps tendon in patients undergoing arthroscopic shoulder surgery: a prospective double-blinded randomized controlled trial. Am J Sports Med 2020; 48: 1439-49.
8. Godenèche A, Kempf JF, Nové-Josserand L, et. al. Tenodesis renders better results than tenotomy in repairs of isolated supraspinatus tears with pathologic biceps. J Shoulder Elbow Surg 2018; 27: 1939-45.
9. Franceschi F, Longo UG, Ruzzini L, Rizzello G, Maffulli N, Denaro V. No advantages in repairing a type II superior labrum anterior and posterior (SLAP) lesion when associated with rotator cuff repair in patients over age 50: a randomized controlled trial. Am J Sports Med 2008; 36: 247-53.
10. Brockmeyer M, Tompkins M, Kohn DM, Lorbach O. SLAP lesions: a treatment algorithm. Knee Surg Sports Traumatol Arthrosc 2016; 24: 447-55.
11. Panossian VR, Mihata T, Tibone JE, Fitzpatrick MJ, McGarry MH, Lee TQ. Biomechanical analysis of isolated type II SLAP lesions and repair. J Shoulder Elbow Surg 2005; 14: 529-34.
12. Erickson BJ, Jain A, Abrams GD, et. al. SLAP lesions: trends in treatment. Arthroscopy 2016; 32: 976-81.
13. Kim SJ, Lee IS, Kim SH, Woo CM, Chun YM. Arthroscopic repair of concomitant type II SLAP lesions in large to massive rotator cuff tears: comparison with biceps tenotomy. Am J Sports Med 2012; 40: 2786-93.
14. Lim S, Kim SK, Kim YS. Comparison between SLAP repair and biceps tenodesis with concomitant rotator cuff repair in patients older than 45 years: minimum 2-year clinical and imaging outcomes. Clin Orthop Surg 2020; 12: 364-370
15. Gilbert F, Böhm D, Eden L, et. al. Comparing the MRI-based Goutallier classification to an experimental quantitative MR spectroscopic fat measurement of the supraspinatus muscle. BMC Musculoskelet Disord 2016; 17: 355.
16. DeOrio JK, Cofield RH. Results of a second attempt at surgical repair of a failed initial rotator-cuff repair. J Bone Joint Surg Am 1984; 66: 563-7.
17. Park MC, Elattrache NS, Ahmad CS, Tibone JE. "Transosseous-equivalent" rotator cuff repair technique. Arthroscopy 2006; 22: 1360.e1-5.
18. Tokish JM, Alexander TC, Kissenberth MJ, Hawkins RJ. Pseudoparalysis: a systematic review of term definitions, treatment approaches, and outcomes of management techniques. J Shoulder Elbow Surg 2017; 26: 177-87.
19. Büyükdoğan K, Koyuncu Ö, Aslan L, Çelik D, Demirhan M. Translation, cross-cultural adaptation, reliability, and validity of Turkish version of the university of California Los Angeles (UCLA) shoulder scale into Turkish. Disabil Rehabil 2021: 1-8.
20. Armstrong A. Diagnosis and clinical assessment of a stiff shoulder. Shoulder Elbow 2015; 7: 128-34.
21. Forsythe B, Guss D, Anthony SG, Martin SD. Concomitant arthroscopic SLAP and rotator cuff repair. J Bone Joint Surg Am 2010; 92: 1362-9.
22. Malavolta E, Yamamoto G, Bussius G, et. al. Establishing minimal clinically important difference for the UCLA and ASES scores after rotator cuff repair. Orthop Traumatol Surg Res 2021: 102894.

23. Civan O, Bilsel K, Kapicioglu M, Ozenci AM. Repair versus biceps tenodesis for the slap tears: A systematic review. J Orthop Surg (Hong Kong) 2021; 29: 23094990211004794.
24. Kanatli U, Ozturk BY, Bolukbasi S. Arthroscopic repair of type II superior labrum anterior posterior (SLAP) lesions in patients over the age of 45 years: a prospective study. Arch Orthop Trauma Surg 2011; 131: 1107-13.
25. van Deurzen DFP, Garssen FL, Wessel RN, Kerkhoffs GMMJ, van den Bekerom MPJ, van Wier MF. The Popeye sign: a doctor's and not a patient's problem. J Shoulder Elbow Surg 2021; 30: 969-76.
26. Lee HJ, Jeong JY, Kim CK, Kim YS. Surgical treatment of lesions of the long head of the biceps brachii tendon with rotator cuff tear: a prospective randomized clinical trial comparing the clinical results of tenotomy and tenodesis. J Shoulder Elbow Surg 2016; 25: 1107-14.
27. Erickson J, Lavery K, Monica J, Gatt C, Dhawan A. Surgical treatment of symptomatic superior labrum anterior-posterior tears in patients older than 40 years: a systematic review. Am J Sports Med 2015; 43: 1274-82.

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Evaluation of the relationship of hemogram parameters with prognosis in older adults with acute abdominal pathologies

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ABSTRACT

Aim: We aimed to investigate the effects of hemogram parameters on the short-term mortality of older adults with acute abdominal pathologies. Secondly, it was aimed to investigate the effect of hemogram parameters on mortality in operated and non-operated patients.

Material and Method: This retrospective observational study was conducted in an emergency medicine clinic between June 1, 2019, and June 1, 2020. Data on patients over 65 years of age who presented to the emergency department with acute abdominal pathologies were analyzed. Hemogram parameters, as in our patient group over 65 years old, who presented with all acute abdomen pathologies; It was examined in terms of its relationship with prognosis in our operated and non-operated patient group. Statistical analysis was performed using SPSS v. 26.0.

Results: The study included a total of 744 patients, of whom 391(52.6%) were women. Mortality was seen in 114(15.32%) patients, and 83(11.2%) patients underwent surgery. AUC and cut off values are for leukocytes count 0.590 and 10.83 for neutrophils count 0.596 and 9.64 for neutrophil-lymphocyte ratio 0.606 and 8.24 to predict mortality (p=0.002, p=0.001, and p>0.001, respectively

Conclusion: In this study, among the hemogram parameters; leukocytes, neutrophils and neutrophil-lymphocyte ratio were determined to have a statistically significant ability to predict mortality in older adults both operaple and non operabl groups groups presenting with acute abdominal pathologies, but their accuracy rates were low.

Keywords: Older adults, leukocytes, neutrophils, lymphocytes, general surgery

INTRODUCTION

The increasing older adults across the world affects hospital systems, discharge rates, and health-related costs. Elective or emergency surgery should be carefully evaluated in older adults. Among patients over 65 years, emergency presentations mostly due to neurological dysfunctions are more common than outpatient clinic presentations. In this patient population, approximately 40% of gastrointestinal operations requiring surgical care occur after emergency presentations (1,2). However, emergency surgical interventions cause a three- to five-fold increase in mortality compared to elective surgery (2,3).

Although comorbidities, medications used, communication difficulties, and insufficient information about a patient's health history are known problems for older adults, the importance of prognostic factors increases with surgical diseases due to the possibility of operation. Hematological parameters have been evaluated in terms of their ability to predict prognoses in many diseases, as well as specifically in the older adults. Red cell distribution width (RDW) (3), hematocrit (HCT) count (4), white blood cell (WBC) count (5), mean corpuscular volume (MCV), hemoglobin (HGB), and neutrophil-lymphocyte ratio (NLR) (6) are among the hemogram parameters that have been individually examined in older adult surgery patients. Acute abdominal pathologies are a frequent reason for admission in older adults. It is important to evaluate the effects of these parameters on the prognosis separately in all older adults, as well as in operated and non-operated older adults, in terms of operation decision.

In this study, we aimed to investigate the effects of hemogram parameters, comorbidities, and findings on the short-term mortality of older adults with acute abdominal pathologies. Secondly, it was aimed to investigate the effect of hemogram parameters on mortality in operated and non-operated patients.

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MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Ümraniye Education and Research Hospital Ethics Committee (Date: 18/03/2020, Decision No: B.10.1.TKH.4.34.H.GP.0.01/62). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This retrospective observational study was conducted in the emergency medicine clinic of Ümraniye Training and Research Hospital between June 1, 2019, and June 1, 2020. Our hospital is a tertiary education and research institute with 836 beds, and it receives 2.8 million presentations per year.

Study Population

Patients over 65 years who presented to our emergency department with acute abdominal pathologies were screened from the hospital computer-based data system (Health Information System [HIS]). According to their survival status, the patients were divided into two groups, either mortality or survivor, and the mortality analysis was performed using the National Death Notification System, which shows all deaths due to all causes in Turkey. Patients under 65 years of age, those with isolated limb or other bone injuries without solid organ injury, and those with missing data or unknown outcomes were excluded from the study.

Data collection

All the patients were examined in terms of demographic data, including age, gender, comorbidities (hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), cerebrovascular disease (CVD) and malignancies, previous history of operation, requirement of surgery at current presentation, symptoms and findings at the time of emergency presentation, diagnoses at the time of hospitalization, hemogram parameters (WBC, neutrophil (NEU), lymphocyte (LYM), HGB, HCT, MCV, and RDW), neutrophil-lymphocyte ratio and clinical outcomes (hospitalization, intensive care admission, referral to an external center, death in the emergency department, and discharge). The relationship between hemogram parameters and mortality in all older adults with a prediagnosis of acute abdomen was investigated. Our patient group was divided into two as operated and non-operated patient groups. The correlation of comorbidity, operation history, symptoms, findings and hemogram parameters with mortality in both groups were evaluated separately. The length of hospital stay was also recorded in the operated and non-operated patient groups.

Statistical Analysis

Statistical analysis was performed using SPSS v. 26.0. The conformity of the variables to normal distribution was examined using visual (histogram and probability charts) and analytical (Kolmogorov-Smirnov test) methods. The normality analysis of continuous data was undertaken using the Shapiro-Wilk test. In the analysis of categorical data, the chi-square test was used and Fisher's exact test was performed when necessary. Chi-square test was used to evaluate the relationship between the operable and non-operable groups and the prognosis. Quantitative variables were presented as median and interquartile range (IQR, 25th–75th percentile) values, and the Mann-Whitney test was used in the analysis of paired groups. For the hemogram parameters; Mann-whitney u test was used. The Spearman correlation test was conducted to investigate the relationship between hemogram parameters and length of hospital stay (LOHS). The receiver-operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic test performance of the investigated parameters in predicting mortality. During this analysis, the area under the curve (AUC) values were calculated, and the sensitivity, specificity, accuracy, and 95% confidence interval (CI) data were analyzed. The AUC values of the parameters were calculated and tested mutually for significance with the DeLong quality test. Statistical significance was accepted as $p < 0.05$.

RESULTS

A total of 744 patients, 391 (52.6%) female, were included in the study. Of all the patients, 114 (15.32%) died. The median age was 77.5 (66–98) years for the mortality group and 77 (66–105) years for of the surviving patients, with no significant difference between the two groups (p=0.389). The baseline characteristics of the patients in the study population are shown in **Table 1** and **Table 2**.

There was no statistically significant relationship between age (p=0.212; p=0.635, respectively) and gender (p=0.917; p=0.187, respectively) and mortality in both operable and non-operable groups. There was a statistically significant correlation between COPD and mortality in the operable group (p=0.002). There was no statistically significant relationship between other comorbid diseases and mortality in both the operable and non-operable groups. There was a statistically significant difference between the patient group presenting with the symptoms of abdominal pain (p=0.001), fever (p=0.026), vomiting (p=0.004), constipation (p=0.045) and syncope (p<0.001) and mortality in the non-operable group. Again in the non-operable group, a significant correlation was found between the findings of abdominal tenderness (p=0.014) and hematochezia (p<0.001) on physical examination and mortality (**Table 3**)

In the mortality group, six (5.3%) patients died during their follow-up in the emergency department, 56 (49.1%) after hospitalization, 14 (12.3%) after admission to intensive care, 15 (13.2%) while in intensive care at an external center, and 23 (20.2%) within 30 days after discharge. There was a statistically significant difference in clinical outcomes according to the comparison of the mortality and survivor groups (p < 0.001), but there was no significant relationship between mortality and LOHS (p= 0.943). Eighty-three (11.2%) of the patients underwent surgery during their follow-up in our hospital. Thirteen (11.4%) of the operable patients died either after hospitalization (n=8; 61.5%) or after admission to the intensive care unit (n=5; 38.5%). There was a significant difference between the operable and non-operated groups in terms of clinical outcomes (p<0.001). While there was a statistically significant relationship between perforation and mortality in the operated group (p<0.001), with the effect of the lower number of patients with perforation in the non-operable group; no statistical significance was found between perforation and mortality (p=0.671). In the non-operable group, there was a statistically significant relationship between patients diagnosed with gastrointestinal bleeding (p=0.001), mesentery ischemia (p=0.013), pancreatitis (p=0.001), decubitus ulcer (p=0.005), Biliary colic (p=0.012), Malignancy (p<0.001) and mortality. There was a significant relationship between WBC (p<0.001; p=0.001, respectively), NEU (p<0.001; p=0.001, respectively), NLR (p<0.001; p=0.002, respectively) and mortality in both operable and non-operable groups. There was statistical significance between HGB (p=0.008) and HTC (p=0.024) and mortality only in the non-operable group. While there was a statistically significant relationship between LOHS and mortality in the operable group (p<0.001); there was no statistically significant relationship between LOHS and mortality in the non-operable group (p=0.468) (**Table 4**).

Revealed a positive correlation between LOHS and WBC, NEU, and NLR (r=0.177, p <0.001; r =0.196, p<0.001; and r=0.205, p<0.001, respectively) while a negative correlation was observed between LYM and LOHS (r =-0.119, p =0.001). The correlation analysis of NLR with LOHS is shown in **Figure 1**.

Table 1. Relationship between the demographic characteristics, comorbidities, symptoms, findings of the older adults surgery patients and their mortality status

	Total	Survivor	Mortality	p
Age (mean,±)	77 (66-105)	77 (66-105)	77.5 (66-98)	0.389
Gender (n,%)				0.228
Female	391 (52.6)	337 (53.5%)	54 (47.4%)	
Male	353 (47.4%)	293 (46.5%)	60 (52.6%)	
Comorbidities (n,%)				
HT	365 (49.1%)	307 (48.7%)	58 (50.9%)	0.673
DM	188 (25.3%)	158 (25.1%)	30 (26.3%)	0.78
CAD	255 (34.3%)	210 (33.3%)	45 (39.5%)	0.204
CKD	68 (9.1%)	54 (8.6%)	14 (12.3%)	0.206
CVD	57 (7.7%)	44 (7%)	13 (11.4%)	0.103
Asthma	3 (0.4%)	3 (0.5%)		0.607
Malignancy	142 (19.1%)	115 (18.3)	27 (23.7%)	0.175
COPD	75 (10.1%)	58 (9.2%)	17 (14.9%)	0.063
History of operation (n,%)	219 (29.4%)	190 (30.2%)	29 (25.4%)	0.309
Symptoms (n,%)				
Abdominal pain	319 (42.9%)	287 (45.6%)	32 (28.1%)	0.001
Fever	53 (7.1%)	50 (7.9%)	3 (2.6%)	0.043
Vomiting	192 (25.8%)	151 (24%)	41 (36%)	0.007
Diarrhea	42 (5.6%)	34 (5.4%)	8 (7%)	0.49
Constipation	107 (14.4%)	95 (15.1%)	12 (10.5%)	0.202
Syncope	12 (1.6%)	4 (0.6%)	8 (7%)	<0.001
Chest pain	19 (2.6%)	17 (2.7%)	2 (1.8%)	0.557
Headache	7 (0.9%)	6 (1%)	1 (0.9%)	0.708
Fatigue	87 (11.7%)	69 (11%)	18 (15.8%)	0.139
Findings (n,%)				
Abdominal tenderness	283 (38%)	249 (39.5%)	34 (29.8%)	0.05
Abdominal guarding	73 (9.8%)	65 (10.3%)	8 (7%)	0.276
Abdominal rebound	17 (2.3%)	14 (2.2%)	3 (2.6%)	0.735
Hematochezia	74 (9.9%)	62 (9.8%)	12 (10.5%)	0.822
Hematemesis	11 (1.5%)	1 (0.2%)	10 (8.8%)	<0.001
Melena	8 (1.1%)	6 (1%)	2 (1.8%)	0.445

Chi-square test was used. HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVD, cerebrovascular disease.

Table 2. Relationship between clinical outcomes, LOHS, clinical diagnoses ,hematological parameters of the older adults surgery patients and their mortality status

	Total	Survivor	Mortality	p
Clinical outcomes (n,%)				<0.001
Hospitalization	418 (56.2%)	362 (57.5%)	56 (49.1%)	
Intensive care admission	43 (5.8%)	29 (4.6%)	14 (12.3%)	
Referral to external center	27 (3.6%)	12 (1.9%)	15 (13.2%)	
Death in emergency department	6 (0.8%)	0	6 (5.3%)	
Discharge	250 (33.6%)	227 (36%)	23 (20.2%)	
LOHS	47.5 (1-2420)	52 (1-2420)	39 (3-741)	0.943
Clinical diagnoses				
Acute appendicitis	26 (3.5%)	23 (3.7%)	3 (2.6%)	0.417
Ileus	77 (10.3%)	68 (10.8%)	9 (7.9%)	0.35
GIS bleeding	70 (9.4%)	50 (7.9%)	20 (17.5%)	0.001
Mesentery ischemia	8 (1.1%)	4 (0.6%)	4 (3.5%)	0.006
Perforation	14 (1.9%)	7 (1.1%)	7 (6.1%)	<0.001
Pancreatitis	59 (7.9%)	59 (9.4%)	0	0.001
Cholecystitis	67 (9%)	62 (9.8%)	5 (4.4%)	0.061
Abscess	15 (3.5%)	11 (2%)	4 (3.5%)	0.218
Hernia	54 (7.3%)	52 (8.3%)	2 (1.8%)	0.014
Multi-trauma	21 (2.8%)	17 (2.7%)	4 (3.5%)	0.631
Diverticulitis	5 (0.7%)	5 (0.8%)	0	0.434
Decubitus ulcer	5 (0.7%)	2 (0.3%)	3 (2.6%)	0.005
Subcutaneous hematoma	8 (1.1%)	7 (1.1%)	1 (0.9%)	0.824
Biliary colic	45 (6%)	44 (7%)	1 (0.9%)	0.012
Cholangitis	23 (3.1%)	19 (3.0%)	4 (3.5%)	0.78
Cholelithiasis/choledocholithiasis	39 (5.2%)	35 (5.6%)	4 (3.5%)	0.367
Malignancy	53 (7.1%)	36 (5.7%)	17 (14.9%)	<0.001
Other	229 (30.8%)	190 (30.2%)	39 (34.2%)	0.388
Hematological parameters				
WBC	10.9 (0.95-95.08)	10.62 (1.93-95.08)	11.8 (0.95-66.17)	0.002
NEU	8.6 (0.59-92.14)	8.43 (1.21-92.14)	9.95 (0.59-62.46)	0.001
LYM	1.2 (0.15-9.54)	1.34 (0.15-9.54)	1.17 (0.28-8.07)	0.027
HGB	12.1 (2.6-19.0)	12.3 (2.6-18.9)	11.2 (4.9-19.0)	0.004
HCT	37.2 (9.0-61.1)	37.5 (9.0-61.1)	35.1 (15.5-58.1)	0.013
MCV	87.8 (55.3-117.2)	87.8 (55.3-117.2)	88.2 (57.1-111.1)	0.726
RDW	28.7 (13.6-38.4)	28.8 (13.6-38.2)	28.3 (17.6-38.4)	0.074
NLR	6.6 (0.75-99.67)	6.17 (0.75-99.67)	8.8 (1.20-66.45)	<0.001
Total	744	630	114	

chi-square test and mann-whitney u were used. LOHS, length of hospital stay; GIS, gastrointestinal system; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; HGB, hemoglobin; HCT,hematocrit; MCV, mean corpuscular volume; RDW, red cell distribution width; NLR,neutrophil/lymphocyte ratio

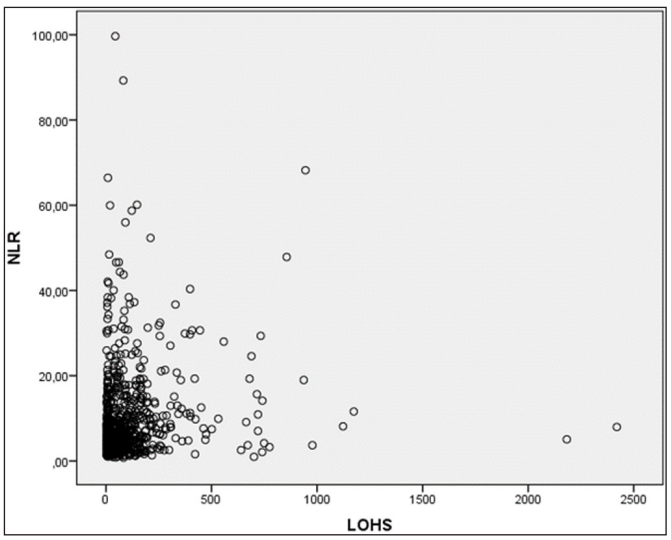

Figure 1. Correlation analysis of NLR with the length of hospital stay

The diagnostic test performance analyses hemogram parameters of WBC, NEU, MCV, RDW, NLR, and LOHS in predicting mortality revealed that WBC, NEU, and NLR were statistically significant in predicting mortality, with the AUC value being calculated as 0.590 (0.553–0.625) for WBC at a cut-off value of 10.83, 0.596 (0.560–0.632) for NEU at a cut-off value of 9.64, and 0.606 (0.569–0.641) for NLR at a cut-off value of 8.24 (p=0.002; p=0.001; and p>0.001, respectively) (**Table 5** and **Figure 2**). When we compared the AUC values of parameters WBC, NEU, and NLR in a pair wise manner using the DeLong quality test, we found no statistically significant difference between these parameters (p=0.386 for WBC vs. NEU; p=0.565 for WBC vs. NLR; and p=0.673 for NLR vs. NEU).

Table 3. Relationship between the demographic characteristics, comorbidities, symptoms, findings of the operable and non-operated patients and their mortality status

	Operable				Non-operated			
	Total	Survivor	Mortality	p	Total	Survivor	Mortality	p
Age (mean,±)	76 (67-96)	76 (67-96)	77 (70-95)	0.212	78 (66-105)	78 (66-105)	78 (66-98)	0.635
Gender (n,%)				0.917				0.187
Female	50 (60.2%)	42 (60.0%)	8 (61.5%)		341 (51.6%)	295 (52.7%)	46 (45.5%)	
Male	33 (39.8%)	28 (40.0%)	5 (38.5%)		320 (48.4%)	265 (47.3%)	55 (54.5%)	
Comorbidities (n,%)								
HT	40 (48.2%)	34 (48.6%)	64 (6.2%)	0.873	325 (49.2%)	273 (48.8%)	52 (51.5%)	0.613
DM	23 (27.7%)	19 (27.1%)	4 (30.8%)	0.788	165 (25.0%)	139 (24.8%)	26 (25.7%)	0.844
CAD	23 (27.7%)	17 (24.3%)	6 (46.2%)	0.106	232 (35.1%)	193 (34.5%)	39 (38.6%)	0.421
CKD	6 (7.2%)	4 (5.7%)	2 (15.4%)	0.514	62 (9.4%)	50 (8.9%)	12 (11.9%)	0.349
CVD	1 (1.2%)	1 (1.4%)	-	-	56 (8.5%)	43 (7.7%)	13 (12.9%)	0.085
Asthma	1 (1.2%)	1 (1.4%)	-	-	2 (0.3%)	2 (0.4%)		0.548
Malignancy	9 (10.8%)	8 (11.4%)	1 (7.7%)	0.691	133 (20.1%)	107 (19.1%)	26 (25.7%)	0.126
COPD	14 (16.9%)	8 (11.4%)	6 (46.2%)	0.002	61 (9.2%)	50 (8.9%)	11 (10.9%)	0.531
History of operation (n,%)	22 (30.8%)	18 (25.7%)	4 (26.5%)	0.705	197 (29.8%)	172 (30.7%)	25(24.8%)	0.228
Symptoms (n,%)								
Abdominal pain	54 (65.1%)	48 (68.6%)	6 (46.2%)	0.12	265 (40.1%)	239 (42.7%)	26 (25.7%)	0.001
Fever	5 (6%)	4 (5.7%)	1 (7.7%)		48 (7.3%)	46 (8.2%)	2 (2.0%)	0.026
Vomiting	19 (22.9%)	16 (23.1%)	3 (22.9%)		173 (26.2%)	135 (24.1%)	38 (37.6%)	0.004
Diarrhea	3 (4.3%)		3 (3.6%)		39 (5.9%)	31 (5.5%)	8 (7.9%)	0.349
Constipation	12 (14.5%)	8 (11.4%)	4 (30.8%)	0.069	95 (14.4%)	87 (15.5%)	8 (7.9%)	0.045
Syncope	1 (1.2%)		1 (7.7%)	0.342	11 (1.7%)	4 (0.7%)	7 (6.9%)	<0.001
Chest pain	1 (1.2%)	1 (1.4%)			18 (2.7%)	16 (2.9%)	2 (2.0%)	0.618
Headache					7 (1.1%)	6 (1.1%)	1 (1.0%)	0.941
Fatigue	7 (8.4%)	4 (5.7%)	3 (23.1%)	0.127	80 (12.1%)	65 (11.6%)	15 (14.9%)	0.358
Findings (n,%)								
Abdominal tenderness	48 (57.8%)	39 (55.7%)	9 (69.2%)	0.365	235 (35.6%)	210 (37.5%)	25 (24.8%)	0.014
Abdominal guarding	26 (31.3%)	21 (30.0%)	5 (38.5%)	0.546	47 (7.1%)	44 (7.9%)	3 (3.0%)	0.079
Abdominal rebound	12 (14.5%)	9 (12.9%)	3 (23.1%)	0.336	5 (0.8%)	5 (0.9%)	0 (0.0%)	0.34
Hematochezia	2 (2.4%)	2 (2.9%)			72 (10.9%)	60 (10.7%)	12 (11.9%)	0.729
Hematemesis					11 (1.7%)	1 (0.2%)	10(9.9%)	<0.001
Melena					8 (1.2%)	6 (1.1%)	2 (2.0%)	0.442

Chi-square test was used. HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVD, cerebrovascular disease.

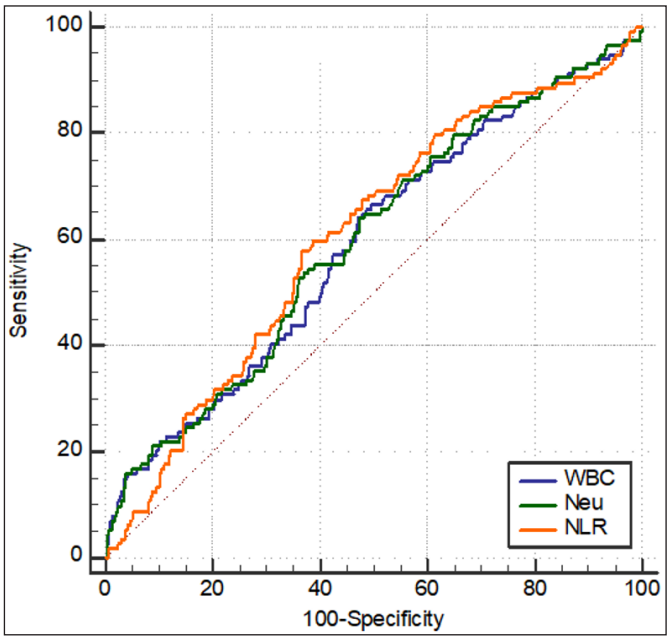

Figure 2. Pairwise comparison of the ROC analysis between WBC, NEU and NLR (DeLong analysis)

DISCUSSION

In this study, WBC, NEU, and NLR were found to be statistically significant in predicting mortality in patients with geriatric surgery indications. When we compared the AUC values of these three parameters, we found no statistically significant difference between them. LYM had a statistically significant relationship with mortality only in the operated group. To the best of our knowledge, there is no other study investigating the relationship between hemogram parameters and mortality in patients presenting to the emergency department with acute abdominal pathologies.

In the literature, older adults have mostly been evaluated in studies undertaken in the fields of gastric or oncological surgery, and the effects of hemogram parameters on postoperative mortality and prognosis have been examined (1). In a study examining factors affecting mortality in older adults undergoing elective surgery, Kim et al. (2) found a statistically significant

Table 4. Relationship between clinical outcomes, clinical diagnoses, hematological parameters, LOHS of the operable and non-operated patients and their mortality status

	Operable				Non-operated			
	Total	Survivor	Mortality	p	Total	Survivor	Mortality	p
Clinical outcomes (n,%)				<0.001				<0.001
Hospitalization	74 (89.2%)	66 (94.3)	8(61.5%)		344 (52.0%)	296 (52.9%)	48 (47.5%)	
Intensive care admission	7 (8.4%)	2 (2.9%)	5 (38.5%)		36 (5.4%)	27 (4.8%)	9 (8.9%)	
Referral to external center					27 (4.1%)	12 (2.1%)	15 (14.9%)	
Death in emergency department					6 (0.9%)		6 (5.9%)	
Discharge	2 (2.4%)	2 (2.9%)			248 (37.5%)	225 (40.2%)	23 (22.8%)	
Clinical diagnoses								
Acute appendicitis	17 (20.5%)	16 (22.9%)	1 (7.7%)	0.213	9 (1.4%)	7 (1.3%)	2 (2.0%)	0.56
Ileus	12 (14.5%)	10 (14.3%)	2 (15.4%)		65 (9.8%)	58 (10.4%)	7(6.9%)	0.287
GIS bleeding	2 (2.4%)	2 (2.9%)		0.537	68 (10.3%)	48 (8.6%)	20 (19.8%)	0.001
Mesentery ischemia	5 (6.0%)	3 (4.3%)	2 (15.4%)	0.122	3 (0.5%)	1 (0.2%)	2 (2.0%)	0.013
Perforation	13 (15.7%)	6 (8.6%)	7 (53.8%)	<0.001	1 (0.2%)	1 (0.2%)	0 (0.0%)	0.671
Pancreatitis	7 (8.4%)	7 (10.0%)		0.517	52 (7.9%)	52 (9.3%)	0(0.0%)	0.001
Cholecystitis	12 (14.5%)	11 (15.7%)	1 (7.7%)	0.45	55 (8.3%)	51 (9.1%)	4 (4.0%)	0.085
Abscess	4 (4.8%)	3 (4.3%)	1 (7.7%)		11 (1.7%)	8 (1.4%)	3 (3.0%)	0.265
Hernia	14 (16.9%)	14 (20.0%)		0.172	40 (6.1%)	38 (6.8%)	2 (2.0%)	0.062
Multi-trauma					21 (3.2%)	17 (3.0%)	4 (4.0%)	0.626
Diverticulitis					5 (0.8%)	5 (0.9%)		0.34
Decubitus ulcer					5 (0.8%)	2 (0.4%)	3 (3.0%)	0.005
Subcutaneous hematoma	1 (1.2%)	1 (1.4%)			7 (1.1%)	6 (1.1%)	1 (1.0%)	0.941
Biliary colic					45 (6.8%)	44 (7.9%)	1 (1.0%)	0.012
Cholangitis					23 (3.5%)	19 (3.4%)	4 (4.0%)	0.775
Cholelithiasis/choledocholithiasis					39 (5.9%)	35 (6.3%)	4 (4.0%)	0.369
Malignancy	4 (4.8%)	4 (5.7%)		0.858	49 (7.4%)	32 (5.7%)	17 (16.8%)	<0.001
Other					229 (34.6%)	190 (33.9%)	39 (38.6%)	0.362
Hematological parameters								
WBC	14.7666 (3.28-95.08)	10.4 (1.93-32.46)	11.7 (0.95-66.17)	<0.001	10.65 (0.95-66.17)	10.4 (1.93-32.46)	11.7 (0.95-66.17)	0.001
NEU	12.5447 (2.45-92.14)	8.26 ((1.21-28.67)	9.93 (0.59-62.46)	<0.001	8.49 (0.59-62.46)	8.26 (1.21-28.67)	9.93 (0.59-62.46)	0.001
LYM	0.77367 (0.20-4.66)	1.5411±0.79401	0.9808±0.42211	0.016	1.28 (0.15-9.54)	1.31 (0.15-9.54)	1.21 (0.28-8.07)	0.157
HGB	12.535 (7.3-18.9)	12.674 ±1.9416	11.785±2.3519	0.146	12.10 (2.6-19)	12.2 (2.6-18.3)	11.1 (4.9-19)	0.008
HCT	38.660 (24.0-53.9)	38.944± 5.5550	37.131±6.8439	0.301	37 (9-61.1)	37.3 (9-61.1)	35.1 (15.5-58.1)	0.024
MCV	87.263 (68.4-99.4)	87.149±6.0365	87.877±3.8739	0.677	87.8 (55.3-117.2)	87.8 (55.3-117.2)	88.2 (57.1-111.1)	0.762
RDW	28.275 (20.3-33.4)	28.353±2.3187	27.854±1.8192	0.465	28.7 (13.6-38.4)	28.8 (13.6-38.2)	28.4 (17.6-38.4)	0.120
NLR	11.1681 (1.30-47.86)	6.045 (0.75-99.67)	8.81 (1.20-66.45)	<0.001	6.35 (0.75-99.67)	6.04 (0.75-99.67)	8.81 (1.2-66.4)	0.002
LOHS	106 (6-1174)	41.50 (1-2420)	35 (3-741)	<0.001	41 (1-2420)	41.5 (1-2420)	35 (3-741)	0.468

As statistical analysis, mann-whitney u was used in parametric data, and chi-square esti was used in non-parametric data. GIS, gastrointestinal WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; RDW, red cell distribution width; NLR, neutrophil/lymphocyte ratio; LOHS, length of hospital stay

Table 5. ROC analysis of hematological parameters and LOHS for 30-day mortality

	AUC	P value	Cut-offvalue	Sensitivity	Specificity	PPV	NPV	Accuracy	95% CI
WBC	0.590	0.002	10.83	65.8	51.4	19.7	89.3	17.22	0.53-0.64
NEU	0.596	0.001	9.64	54.4	62.4	20.7	88.3	16.77	0.53-0.65
MCV	0.510	0.736	88.9	48.2	58.3	17.3	86.2	6.5	0.45-0.57
RDW	0.553	0.074	29	65.79	45.87	18	88.1	11.6	0.39-0.50
NLR	0.606	<0.001	8.24	57.9	63.3	22.2	89.3	21.23	0.55-0.66
LOHS	0.502	0.940	53	38.6	50.3	12.3	81.9	11.09	0.44-0.55

ROC, receiver operating characteristic; LOHS, length of hospital stay; AUC, area under the curve;PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; WBC, white blood cell; NEU, neutrophil; MCV, mean corpuscular volume; RDW, red cell distribution width; NLR, neutrophil/lymphocyte rat

relationship between high WBC and low HGB and mortality. In a study investigating acute kidney injury after Cardiac surgery in older adults, it was determined that HGB values were statistically significantly correlated with the development of acute kidney injury (7). In another study that examined older adults undergoing non-cardiac surgery, a statistically significant difference was detected between decreased preoperative HCT levels and borderline polycythemia and 30-day mortality (8). In our study population, there was a statistically significant relationship between WBC elevation, low HGB and HTC levels, and mortality. While no statistically significant difference was observed in the HGB and HCT values of the operable and non-operated groups, WBC was significantly higher in the former.

The effect of RDW levels on prognosis has been investigated regarding many diseases as well as specifically in the older adults. Liu et al. (3) who examined 1,891 older adults after percutaneous coronary intervention, observed that mortality was higher in those with high RDW levels. In a study by Abdullah et al. (4), older adults who underwent non-cardiac surgery were included in the sample, and a statistically significant relationship was found between serious RDW elevation and anemia and mortality. In another study, Ichinose et al. (5) evaluated patients who underwent resection for small cell lung cancer, the effect of RDW on mortality for older adults did not change according to age, which is similar to our study; however, a high RDW level without anemia was determined to be more prognostic than a high RDW level accompanied by anemia. It is difficult to decide whether to perform surgery in older adults. However, as far as we know, there is no study examining older adults who presented with acute abdominal pathologies and who were not operated for reasons such as comorbidity and age. In a study investigating the relationship between mortality after hip fracture surgery and pre-treatment RDW levels, 203 older adults were examined and RDW levels were found to be statistically significantly higher in the mortal group (9). On the other hand, in a study examining the results of conservative approach to osteoporotic vertebral fractures, mortality was found to be significantly higher in older adults with high RDW levels compared to older adults with normal RDW levels (10). In the current study, no statistically significant relationship was observed between RDW levels and mortality in any of the patient groups, regardless of operation status.

In addition to HGB, HTC and RDW levels, NLR has also taken its place in older adults surgery patients in the literature, but as with other hemogram parameters, the prognosis was evaluated only in operated patients. Ichinose et al. (5) reported a relationship between NLR elevation and morbidity. In a study investigating mortality after emergency abdominal surgery, NLR was the best predictor in determining mortality (6). Similarly, Cigsar et al. (11) examined 755 patients who underwent laparotomy for acute appendicitis and found that NLR could predict appendectomy in the adults patient group but not in the older adults patient group. Complications have also been investigated in terms of; In a study examining the development of anastomotic leakage after colorectal surgery, no statistical significance was found between the NLR level and the development of anastomotic leakage (12). The results of our study revealed a positive correlation between NLR and LOHS in all patient groups, regardless of operation status, and there was a significant correlation between the level of this parameter and mortality.

The literature confirms that comorbidities and medications such as those related to hemogram parameters negatively affect the treatment process of elderly patients followed up for surgical diseases. In a study examining the prognosis after acute cholecystitis treatment in older adults, 1075 patients were examined and the patients were divided into 2 groups receiving medical and surgical treatment. While there was no difference between the groups in terms of mortality and major complications; Patients with congestive heart failure were significantly higher in the group receiving medical treatment (13). Kim et al. (2) investigated postoperative mortality in older adults and found a statistically significant difference in mortality according to the presence of cancer and stroke but detected no statistically significant relationship between DM, HT, and ischemic heart disease and mortality. In the studies of Wei-Hsiang et al. (9) on hip fracture operations, the relationship between diabetes and hypertension and mortality was statistically insignificant. We determined that mortality was statistically significantly related only to COPD ($p=0.002$) in the operable group, and there was no clinically significant relationship between any of the comorbidities and mortality when the entire patient group was taken into consideration.

Besides comorbidities, we know that age can affect surgical decision making in older adults. In a study of head and neck cancers, Stepherd et al. (14) found that age alone had no effect on postoperative mortality, complications, and length of hospital stay. Cost is also considered in deciding on surgery. Rao et al. (15), in a study in which they analyzed the cost and mortality in rectal cancers, emphasized that it is necessary to be more careful when deciding on surgery in older adults. In addition to the evaluation of hemogram parameters, this study examined the older adults according to whether they were approved for surgery or considered inoperable. In the literature, mortality analyses were

mostly performed in studies on gastric or tumor surgery, and surgical decision differs according to the stages of the disease or diagnosis (14,15). However, acute abdominal pathologies may not always require surgery. In our study, there was no statistically significant relationship between operation status and mortality, suggesting that the surgical decision was made in cases where risk factors decreased.

Limitations

The single-center design of our study is a serious limitation. Differences in the diagnoses of the patients also limited the comparisons performed according to operation status. Lastly, we compared short-term mortality according to only emergency surgery operations, and we did not have data on elective surgeries scheduled to be performed 30 days after presentation. Another limitation of this study was we couldn't compare the medications of patients between groups that may affect the results of study.

CONCLUSION

In this study, WBC, NEU, and NLR were determined to have a statistically significant ability to predict mortality in older adults presenting with acute abdominal pathologies, but their accuracy rates were low. When the AUC values were compared, there was no statistically significant difference between these three parameters, but NLR was superior to WBC and NEU in predicting mortality. Besides, since there was no difference in the results in the operated and non-operated groups, we can say that an operation decision cannot be made with only NLR values.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ümraniye Education and Research Hospital Ethics Committee (Date: 18/03/2020, Decision No: B.10.1.TKH.4.34.H.GP.0.01/62).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Davis P, Hayden J, Springer J, Bailey J, Molinary M, Jhonson P. Prognostic factors for morbidity and mortality in elderly patients undergoing acute gastrointestinal surgery: a systematic review. Can J Surg 2014; 57: E44–E52.
2. Kim K, Park K, Koo K, Han H, Kim C. Comprehensive geriatric assessment can predict postoperative morbidity and mortality in elderly patients undergoing elective surgery. Archives of Gerontology and Geriatrics 2013; 56: 507-12.
3. Liu X-M, Ma C-S, Liu X-H, et al. Relationship between red blood cell distribution width and intermediate-term mortality in elderly patients after percutaneous coronary intervention. J Geriatr Cardiol 2015; 12: 17–22.
4. Abdullah HR, Sim YE, Sim YT, et al. Preoperative red cell distribution width and 30-day mortality in older patients undergoing non-cardiac surgery: a retrospective cohort observational study. Sci Rep 2018; 8: 6226.
5. Ichinose U, Murakawa T, Kawashima M, et al. Prognostic significance of red cell distribution width in elderly patients undergoing resection for non-small cell lung cancer. J Thorac Dis 2016; 8: 3658–66.
6. Vaughan-Shaw PG, Rees JRE, King AT. Neutrophil lymphocyte ratio in outcome prediction after emergency abdominal surgery in the elderly. Int J Surg 2012; 10: 157-62.
7. Verwijmeren L, Bosma M, Vernooij LM, et al. Associations between preoperative biomarkers and cardiac surgery–associated acute kidney injury in elderly patients: a cohort study. Anesth Analg 2021; 133: 570-7.
8. Wu W, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007; 297: 2481-8.
9. Wei-Hsiang H, Zhu Y, Zhang J, Zhang Y. Pretreatment red blood cell distribution width as an efficient predictor of survival in older patients undergoing hip fracture surgery. Int J Clin Pract 2021; 00: e14791.
10. Sakai Y, Wakao N, Matsui H, Watanabe T, Lida H, Katsumi A. Elevated red blood cell distribution width is associated with poor outcome in osteoporotic vertebral fracture. J Bone Miner Metab 2021; 39: 1048-57.
11. Cigsar G, Yıldırım AC, Anuk T, et al. Neutrophil to lymphocyte ratio on appendectomy of geriatric and nongeriatric patients. J Invest Surg 2017; 30: 285-90.
12. Pantoja Pachajoa DA, Gielis M, Palacios Huatuco RM, et al. Annals of medicine and surgery neutrophil-to-lymphocyte ratio vs c-reactive protein as early predictors of anastomotic leakage after colorectal surgery: a retrospective cohort study. Ann Med Surg (Lond) 2021; 64: 102-201.
13. Rosa F, Covino M, Cozza V, et al. Management of acute cholecystitis in elderly patients: A propensity score-matched analysis of surgical vs. medical treatment. Dig Liver Dis 2021; 53: 1620-6.
14. Shepherd SJ, Creber N, Mansour K, Wiesenfeld D, Iseli TA, Amott D. Relationship between age, comorbidities and complications in head and neck cancer patients undergoing curative surgery. ANZ J Surg 2020; 90: 851-5.
15. Rao C, Sun Myint A, Athanasiou T, et al. Avoiding radical surgery in elderly patients with rectal cancer is cost-effective. Dis Colon Rectum 2017; 60: 30-42.

Original Article

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The attitudes and beliefs of physiotherapists, family physicians and physiatrists concerning chronic low back pain

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ABSTRACT

Objective: To examine the chronic low back pain (CLBP)-related attitudes and beliefs of primary and secondary healthcare professionals responsible for the treatment of this condition.

Material and Method: The study was conducted with 40 family physicians, 30 physiatrists, and 40 physiotherapists. The beliefs and attitudes of the participants concerning CLBP were evaluated using the Back Belief Questionnaire (BBQ), Health Care Providers' Pain and Impairment Relationship Scale (HC-PAIRS), and Pain Attitudes and Beliefs Scale for Physiotherapists (PABS-PT).

Results: Among all the participants, the rate of those with predominantly biomedical beliefs was 80.9%, while the rate of those with predominantly biopsychosocial beliefs was 15.5%. In addition, it was observed that the BBQ, HC-PAIRS and PABS-PT scores were not affected by educational status, number of patients with CLBP treated or examined in a week, and years of experience ($p>0.05$). The BBQ and HC-PAIRS scores of the family physicians were statistically significantly lower compared to the physiotherapists and those of the physiotherapists were statistically significantly lower compared to the physiatrists ($p<0.05$). However, the PABS-PT scores were similar among different healthcare professionals ($p>0.05$).

Conclusion: This study revealed that family physicians, physiotherapists, and physiatrists in Turkey might have negative attitudes and beliefs concerning CLBP and the biopsychosocial approach should be further adopted among healthcare professionals.

Keywords: Chronic low back pain, attitudes and beliefs, healthcare professionals, physiotherapists, family physicians, physiatrists

INTRODUCTION

Chronic low back pain (CLBP) is an important public health problem going beyond the repair process and recovery of the biological function of tissues, in which the underlying pathology is not fully understood and complaints last for more than three months. CLBP is the second leading cause of disability and constitutes an economic problem globally (1). CLBP reduces productivity, resulting in a significant loss of work force and placing a large economic burden on all countries. Immobilization, postural deformities, smoking, occupation, educational level, inactivity/sedentary life, obesity, not paying attention to body biomechanics, age, and psychological and psychosocial factors play a role in the etiology of CLBP (2,3). Negative changes are observed in people's daily life activities, quality of life and functional movement due to the progression of acute pain to chronic pain; i.e., prolongation of pain experience. In these people, fear avoidance reactions develop as a result of the belief that pain will occur or increase in response to movement or activity, and therefore people begin to avoid such activity (4). People who continue their lives with the fear of movement try to avoid the possibility of new disability or repetition of disability (5). As a result, they limit their activity levels and adopt a more sedentary lifestyle (6). Pain and avoidance behaviors, which emerge through the reduction of physical activities, play an important role in the etiopathogenesis of CLBP (7). Therefore, the attitudes and beliefs of patients with CLBP and those of healthcare professionals providing care for these patients also affect the therapeutic process (8). Patients with chronic pain are in constant interaction with healthcare professionals for their treatment. Healthcare professionals make recommendations for their patients throughout the treatment process. These recommendations vary according to the beliefs and

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attitudes of healthcare professionals, and as a result treatment programs that determine the activity levels of patients differ from person to person. Thus, patients are affected by the attitudes and beliefs of healthcare professionals who plan and apply their pain-related treatments (9-11).

Healthcare professionals' attitudes and beliefs concerning chronic pain can be categorized into two approaches as biomedical and biopsychosocial. According to the biomedical model, pain and disability occur as a result of physical damage. In the biomechanical approach, the healthcare professional designs his/her treatment according to pain area. The priority of treatment is to detect and eliminate the damaging factor causing pain. However, the level of disability in patients with chronic pain cannot be fully explained by the degree of physical damage. At this stage, the biopsychosocial approach model becomes comes into play. According to this model, symptoms emerge and become chronic under the influence of psychological and social factors; therefore, pain can occur without any physical damage. In this approach, the treatment should be arranged by considering the social environment and psychological factors of the patient (12-15).

Parallel to the developments in pain science, the biomedical approach being more predominant than the biopsychosocial approach among healthcare professionals is accepted as a negative belief and attitude (13). Negative beliefs and attitudes of healthcare professionals concerning low back pain can lead to the development of CLBP problems in patients and inability to effectively use pain control or reactivation strategies. Healthcare professionals with such attitudes also encourage patients' negative perceptions of the disease by advising them to protect the spine, rest in bed, stay away from work, or limit normal activities, resulting in more disability and unnecessary consultations in the investigations of the disease (16). There is evidence that educational strategies to change the beliefs of patients and healthcare professionals concerning low back pain can reduce this pain and associated disability (17,18). In this context, the attitudes and beliefs of primary and secondary healthcare professionals are of great importance in order to appropriately guide patients presenting to health institutions and treat those with CLBP more effectively. However, to the best of our knowledge, there is no comprehensive study examining the CLBP-related beliefs and attitudes of healthcare professionals in different disciplines in Turkey. Therefore, in this study, we aimed to examine the related attitudes and beliefs of healthcare professionals that provide primary and secondary care and are responsible for the treatment of CLBP.

MATERIAL AND METHOD

This research, planned as a multicenter, cross-sectional study, was carried out with the permission of Kütahya University Non-interventional Clinical Research Ethics Committee (Date: 22.12.2020, Decision No: 2020/18-03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was carried out between January and May 2021 at 14 different family health centers in Kutahya, Physical Therapy and Rehabilitation Department of Kutahya Health Sciences Hospital, and Yoncali Physical Therapy and Rehabilitation Hospital. Family physicians, physiatrists, and physiotherapists aged 21-65 years, who volunteered to participate in the study, worked actively, had clinical experience with low back pain, were included in the study. All the participants were informed about the study, and their informed consent was obtained. The descriptive data of the participants, including their occupation, age, educational status, number of patients with CLBP seen in a week, and years of experience were questioned with a previously prepared form. Then, the participants completed the Back Belief Questionnaire (BBQ), Health Care Providers' Pain and Impairment Relationship Scale (HC-PAIRS), and Pain Attitudes and Beliefs Scale for Physiotherapists (PABS-PT).

Back Belief Questionnaire

The BBQ is used to evaluate participants' expectations concerning negative conditions that may occur as a result of low back pain, their approach to returning to work, and their attitudes and beliefs concerning recovery. The items are based on a five-point Likert scale with the responses ranging from 'strongly disagree=1' to 'strongly agree=5', and the total score varies between 9 and 45 points. Low scores indicate more maladaptive and pessimistic beliefs concerning low back pain. The Turkish version of scale was adopted by Karaman and Kucukakkas (19) and they found that it is valid and reliable.

Health Care Providers' Pain and Impairment Relationship Scale

The HC-PAIRS is a scale used to evaluate attitudes and beliefs in the clinic to examine the effects of healthcare providers on the clinical management of patients' low back pain status. The items measure four different concepts, functional expectations, social expectations, need for treatment, and predicted cognition, based on a seven-point Likert scale ranging from '1=strongly disagree' to '7=strongly agree'. The total score varies between 12 and 84 points. High scores indicate that the healthcare professional strongly believes that low

back pain is a cause of disability and tends to encourage patients to limit their activities to reduce low back pain. In other words, as the total score increases, the negative attitudes and beliefs of healthcare professional toward low back pain also increase. Aksoy et al. (20) found that the Turkish version of HC-PAIRS is reliable and valid.

Pain Attitudes and Beliefs Scale for Physiotherapists

The PABS-PT is used to determine the attitudes and beliefs of healthcare professionals concerning pain based on the biomedical and biopsychosocial approaches. Seven of the 13 items of the scale represent the biomedical approach of healthcare approaches; i.e., the belief that if pain increases, tissue damage will also increase based on the relationship between tissue damage and pain, while the remaining six items represent the biopsychosocial approach of healthcare professionals; i.e., in addition to tissue damage, psychological factors can also cause pain. Two scores are obtained from the scale as Factor 1 (biomedical approach) and Factor 2 (biopsychosocial approach), with the total scores ranging from 7 to 42 for the former and 6 to 36 for the latter. Depending on which score is higher, the likely treatment approach of the healthcare professional is interpreted as biomedically or biopsychosocially oriented. The Turkish version of PABS-PT was performed by Dalkilinc et al. (21) and they found that it is valid and reliable.

Statistical Analysis

Obtained data were analyzed using IBM SPSS v. 22 (IBM, Armonk, NY, USA) software package. Tukey's non-additivity test was used to determine whether the items in the scales were perceived the same by the participants, and Hotelling's T-square test was conducted to determine whether the items were prepared in a way to form an additive scale. The presence of a possible multi-connection problem was explored by examining the tolerance and Variance Inflation Factor (VIF) values. The sociodemographic data of the participants were presented as frequency (n) and percentage (%), mean, standard deviation, and minimum and maximum values. In addition, a regression analysis was performed to examine the effects of educational level, number of patients with CLBP seen in a week, and years of experience on the scale scores. One-way analysis of variance (ANOVA) was used to compare the demographic data and scale scores between different occupational groups. Accordingly, a multiple comparison method (post-hoc, Tukey HSD) was applied to determine which occupational groups caused significant differences. The statistical significance level was accepted as $p<0.05$.

RESULTS

The study was concluded with 110 volunteer healthcare professionals, including 40 family physicians, 30 physiatrists, and 40 physiotherapists (**Figure 1**). Table 1 presents the sociodemographic data of the participants, such as age, sex, educational level, years of experience, and number of patients with low back pain seen in a week. **Table 2** gives the internal consistency coefficients of the scales used in the study. The mean scores of the participants were 31.57±5.70 for BBQ, 54.21±8.62 for HC-PAIRS, 28.70±5.52 for the biomedical factor of PABS-PT, and 21.84±0.84 for the biopsychosocial factor of PABS-PT. Among all the participants, the rate of those with predominantly biomedical beliefs was 80.9% and the rate of those with predominantly biopsychosocial beliefs was 15.5%. Both approaches were equally present in 3.6% of the participants. According to the regression analysis, educational level, number of patients with CLBP seen in a week, and years of experience did not affect the participants' beliefs and attitudes concerning low back pain ($p>0.05$).

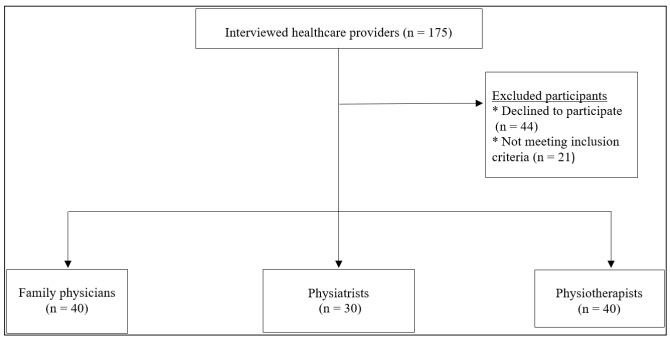

Figure 1. Flow chart of the participants

Table 1. Characteristics of the participants

	(n=110) (Mean±SD)
Age (years)	40.55±10.89
Experience (years)	15.68±10.73
Number of patients seen per week	20.54±20.32
Sex	**n (%)**
Female	51(46.4)
Male	59 (53.6)
Education	**n (%)**
Bachelor of science	32 (29.1)
Master of science	52 (47.3)
Doctorate	26 (23.6)

n: number of participants, SD: standard deviation

Table 2. Cronbach alpha coefficients of the scales

Outcomes	Cronbach alpha coefficient
BBQ	0.72
HC-PAIRS	0.76
PABS-PT	0.71

BBQ: Back Belief Questionnaire, HC-PAIRS: Health Care Providers' Pain and Impairment Relationship Scale, PABS-PT: Pain Attitudes and Beliefs Scale for Physiotherapists

When the participants were compared according to different occupational groups, there was no significant difference in relation to sex (p=0.540), mean age (p=0.180), years of experience (p=0.551) and number of patients with CLBP seen in a week (p=0.290). However, a significant difference was observed between the occupational groups in terms of education levels (p<0.001). The physiotherapists had the lowest educational level, while the physiatrists had the highest educational level. According to the results of one-way ANOVA, the physiotherapists had significantly lower BBQ scores than the physiotherapists [p=0.029; 95% confidence interval (CI): (-3.820)-(1.170)], and the physiotherapists had lower BBQ scores than the physiatrists [p=0.050; 95% CI: (−5.395)-(-0.004)]. Similarly, the HC-PAIRS scores of the family physicians were significantly higher compared to the physiotherapists [p=0.049; 95% CI: (-3.513-3.963)], and those of the physiotherapists were significantly higher compared to the physiatrists (p=0.021; 95% CI: (0.412-10.321). There was no significant difference between the occupational groups in relation to PABS-PT Factor 1 and Factor 2 scores (p>0.05) (**Table 3**).

DISCUSSION

This study was planned to examine the CLBP-related attitudes and beliefs of healthcare professionals, namely family physicians, physiatrists, and physiotherapists actively working in primary and secondary healthcare institutions and completed with 110 participants. It was concluded that biomedical beliefs were more dominant than biopsychosocial beliefs in all occupational groups examined in the study. When the beliefs and attitudes of the participants were examined according to their occupational groups, it was determined that pessimistic beliefs concerning CLBP were more common among the family physicians compared to the physiotherapists, and among the physiotherapists compared to the physiatrists. In addition, the belief that low back pain causes disability and activity limitation was at the strongest level among the family physicians and lowest level among the physiatrists. The biomedical and biopsychosocial beliefs concerning CLBP were similar between the occupational groups.

Many researchers suggested that factors such as the educational level of healthcare professionals, clinical experience, and number of patients treated may affect their treatment approach and choices (12-15). In contrast, Alshehri et al. (22), examining the relationship between the educational level of healthcare professionals and their CLBP-related attitudes and beliefs, concluded that educational level did not have an effect on the PABS-PT scores. Innes et al. (23) determined that the number of patients treated had no effect on the chiropractors' biomedical or biopsychosocial beliefs and attitudes concerning CLBP. In another study (24), as the number of patients with low back pain seen by physiotherapists on a monthly basis decreased the belief that low back pain causes disability and activity limitation increased. In our study, according to the results of the three scales, we observed that the educational level, clinical experience, and number of patients seen in a week did not have anu effect on the CLBP-related beliefs and attitudes of the family physicians, physiotherapists and physiatrists. In light of these contradictory results, the effects of education, clinical experience, and number of treated patients on the beliefs and attitudes of healthcare professionals remain unclear.

In the literature, many studies have compared the beliefs and attitudes of different occupational groups and reported different results. In a study by Sit et al. examining the approach of family physicians and practitioners with PABS-PT (25), it was found that family physicians had less biomedical beliefs than general practitioners. In contrast, in another study by Bishop et al. (8), in which the beliefs and attitudes of physiotherapists and general practitioners were compared using PABS-PT, no significant difference was found between the occupational groups. Rainville et al. (26) investigated the beliefs and attitudes of phyisicans, physiotherapists, occupational therapists, psychologists, and nurses concerning low back pain using HC-PAIRS. The authors concluded that physicians and nurses had a stronger belief that low back pain causes disability and activity limitation than physiotherapists and occupational therapists. In another study (27) evaluating the attitudes and beliefs of senior students in physiotherapy and rehabilitation, medicine, and nursing using BBQ, physiotherapy

Table 3. Scores of pain attitudes and beliefs

Outcome measures	Family physicians (Mean±SD)	Physiotherapists (Mean±SD)	Physiatrists (Mean±SD)	F (p)
BBQ	30.07±5.92	31.52±6.08	34.10±3.93	4.59 (0.01*)
HC-PAIRS	56.12±8.33	55.05±7.81	50.56±8.74	4.58(0.01*)
PABS-PT Factor 1	28.97±5.03	29.07±6.24	27.56±5.50	0.74 (0.48)
PABS-PT Factor 2	21.72±4.79	22.85±4.01	22.26±4.25	1.25 (0.29)

BBQ: Back Belief Questionnaire, HC-PAIRS: Health Care Providers' Pain and Impairment Relationship Scale, PABS-PT: Pain Attitudes and Beliefs Scale for Physiotherapists SD: standard deviation, F: Analysis of variance statistics, p: significance level; *p<0.05

students were found to have more positive beliefs compared to medical and nursing students. Similarly, in a study conducted with a total of 4,964 health science students studying at various departments, including medicine, physiotherapy, chiropractic, osteopathy, nursing, and pharmacy, Lewis and Battaglia (28) reported that physiotherapy and rehabilitation students had more positive beliefs than those studying in the remaining disciplines. In the current study, we observed more pessimistic beliefs concerning CLBP among the family physicians compared to the physiotherapists, and among the physiotherapists compared to the physiatrists based on the BBQ scores. In addition, in terms of the HC-PAIRS scores, the belief that low back pain causes disability and activity limitation was the strongest in the family physicians and lowest among the physiatrists. For PABS-PT, there was no significant difference between the occupational groups in terms of the biomedical and biopsychosocial factors, but biomedical beliefs were predominant in all occupational groups. In brief, studies conducted to date have generally revealed that attitudes and beliefs concerning CLBP may differ according to occupations.

There are certain limitations to our study. Vocational courses or training on pain attended by the participants were not questioned. Similarly, the back pain experiences of the participants themselves were not evaluated. Since these factors are considered to affect attitudes and beliefs concerning CLBP, future studies can be planned to investigate the effects of these factors. Besides, the examining of the attitudes and beliefs of other health care professionals such as neurosurgeons would have great importance in such a study.

According to the results of our study, healthcare professionals should review their attitudes and beliefs concerning CLBP, which places a great economic burden on countries across the world and should especially focus on the biopsychosocial approach. All healthcare professions involved in CLBP, especially family physicians who play a key role in primary care, and physiatrists and physiotherapists providing secondary care should follow the current literature on chronic pain science or participate in vocational training and meetings on this subject to help spread biopsychosocial beliefs. This will shorten the treatment process of patients, and thus reduce costs related to this health problem, which constitutes a significant part of health expenditures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kütahya University Non-interventional Clinical Research Ethics Committee (Date: 22.12.2020, Decision No: 2020/18-03).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Allegri M, Montella S, Salici F, et al. Mechanisms of low back pain: a guide for diagnosis and therapy. F1000Res 2016; 5: F1000 Faculty Rev-1530.
2. Glombiewski JA, Hartwich-Tersek J, Rief W. Two psychological interventions are effective in severely disabled, chronic back pain patients: a randomised controlled trial. Int J Behav Med 2010; 17: 97-107.
3. Manchikanti L, Singh V, Falco FJ, Benyamin RM, Hirsch JA. Epidemiology of low back pain in adults. Neuromodulation 2014; 17: 3-10.
4. Trinderup JS, Fisker A, Juhl CB, Petersen T. Fear avoidance beliefs as a predictor for long-term sick leave, disability and pain in patients with chronic low back pain. BMC Musculoskelet Disord 2018; 19: 1-8.
5. Turk DC, Wilson HD. Fear of pain as a prognostic factor in chronic pain: conceptual models, assessment, and treatment implications. Curr Pain Headache Rep 2010; 14: 88-95.
6. Lundberg M, Larsson M, Ostlund H, Styf J. Kinesiophobia among patients with musculoskeletal pain in primary healthcare. J Rehabil Med 2006; 38: 37-43.
7. van der Hulst M, Vollenbroek-Hutten MM, Rietman JS, Hermens HJ. Lumbar and abdominal muscle activity during walking in subjects with chronic low back pain: support of the "guarding" hypothesis?. J Electromyogr Kinesiol 2010; 20: 31-38.
8. Bishop A, Foster NE, Thomas E, Hay EM. How does the self-reported clinical management of patients with low back pain relate to the attitudes and beliefs of health care practitioners? A survey of UK general practitioners and physiotherapists. Pain 2008; 135: 187-95.
9. Bishop A, Thomas E, Foster NE. Health care practitioners' attitudes and beliefs about low back pain: a systematic search and critical review of available measurement tools. Pain 2007; 132: 91-101.
10. Fullen BM, Baxter GD, Doody C, Daly LE, Hurley DA. General practitioners' attitudes and beliefs regarding the management of chronic low back pain in Ireland: a cross-sectional national survey. Clin J Pain 2011; 27: 542-9.
11. Macdonald M, Vaucher P, Esteves JE. The beliefs and attitudes of UK registered osteopaths towards chronic pain and the management of chronic pain sufferers: a cross-sectional questionnaire based survey. Int J Osteopath Med 2018; 30: 3-11.
12. Daykin AR, Richardson B. Physiotherapists' pain beliefs and their influence on the management of patients with chronic low back pain. Spine 2004; 29: 783-95.
13. Houben RM, Vlaeyen JW, Peters M, Ostelo RW, Wolters PM, Stomp-van den Berg SG. Health care providers' attitudes and beliefs towards common low back pain: factor structure and psychometric properties of the HC-PAIRS. Clin J Pain 2004; 20: 37-44.

14. Ostelo RW, Stomp-van den Berg SG, Vlaeyen JW, Wolters PM, de Vet HC. Health care provider's attitudes and beliefs towards chronic low back pain: the development of a questionnaire. Man Ther 2003; 8: 214-22.
15. Overmeer T, Boersma K, Main CJ, Linton SJ. Do physical therapists change their beliefs, attitudes, knowledge, skills and behaviour after a biopsychosocially orientated university course?. J Eval Clin Pract 2009; 15: 724-32.
16. Liddle SD, Baxter GD, Gracey JH. Chronic low back pain: patients' experiences, opinions and expectations for clinical management. Disabil Rehabil 2007; 29: 1899-909.
17. Coudeyre E, Tubach F, Rannou F, et al. Fear-avoidance beliefs about back pain in patients with acute LBP. Clin J Pain 2007; 23: 720-5.
18. Buchbinder R, Jolley D. Effects of a media campaign on back beliefs is sustained 3 years after its cessation. Spine 2005; 30: 1323-30.
19. Arifoğlu Karaman Ç, Küçükakkaş O. Cross-cultural adaptation and validation of the Back Beliefs Questionnaire to the Turkish language. Disabil Rehabil 2021; 43: 1917-23.
20. Caner Aksoy C, Saracoglu I, Akkurt L. Turkish version of health care providers' pain and impairment relationship scale: Reliability and validity. Musculoskelet Sci Pract 2021; 53: 102367.
21. Dalkilinc M, Cirak Y, Yilmaz GD, Parlak Demir Y. Validity and reliability of Turkish version of the Pain Attitudes and Beliefs Scale for Physiotherapists. Physiother Theory Pract 2015; 31: 186-93.
22. Alshehri MA, Alzahrani H, Alotaibi M, Alhowimel A, Khoja O. Physiotherapists' pain attitudes and beliefs towards chronic low back pain and their association with treatment selection: a cross-sectional study. BMJ Open 2020; 10: e037159.
23. Innes SI, Werth PD, Tuchin PJ, Graham PL. Attitudes and beliefs of Australian chiropractors' about managing back pain: a cross-sectional study. Chiropr Man Therap 2015; 23: 17.
24. Magalhães MO, Costa LO, Cabral CM, Machado LA. Attitudes and beliefs of Brazilian physical therapists about chronic low back pain: a cross-sectional study. Rev Bras Fisioter 2012; 16: 248-53.
25. Sit RW, Yip BH, Chan DC, Wong SY. Primary care physicians' attitudes and beliefs towards chronic low back pain: an Asian study. PLoS One 2015; 10: e0117521.
26. Rainville J, Bagnall D, Phalen L. Health care providers' attitudes and beliefs about functional impairments and chronic back pain. Clin J Pain 1995; 11: 287-95.
27. Kennedy N, Healy J, O'Sullivan K. The Beliefs of third-level healthcare students towards low-back pain. Pain Res Treat 2014; 2014: 675915.
28. Lewis KL, Battaglia PJ. Knowledge of psychosocial factors associated with low back pain amongst health science students: a scoping review. Chiropr Man Therap 2019; 27: 1-15.

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Effects of defensive medicine practices on health care in southeast Turkey

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ABSTRACT

Aim: In our country, the stress experienced by physicians due to their working conditions and intense workload plays a role in the formation of medical errors, therefore, physicians want to protect themselves from litigation processes with defensive medicine practices. The aim of our study is to evaluate the effects of defensive medicine practices on health service delivery.

Material and Method: In our study, the knowledge and attitudes of a total of 175 dentists working in Dicle University Faculty of Dentistry and Diyarbakir Oral and Dental Health Hospital and its affiliated centers about defensive medicine practices, age, physician (service) duration, gender, institution, title and specialty areas, if any, the relationship was examined using the knowledge level measurement questionnaire. While performing statistical analysis, Chi-square Test was used for comparisons.

Result: It was observed that 32% of the physicians in the 26-40 age group, who constitute the vast majority (71.4%) of the participants in the study, were not aware of the concept of defensive medicine. It was found that 36.6% of the participants, 84.4% of those with 1-5 years of medical experience, and 83.3% of the specialty students with the largest share, with the largest share, did not know this concept at all.

Conclusion: It is found that most of the physicians do not have the necessary knowledge about medical errors and malpractice. While the level of knowledge is increased through in-service training programs, seminars and conferences about malpractice, medical errors, defensive medicine practices, the experience of experienced physicians can be used in preventing and solving problems.

Keywords: Malpractice, defensive medicine practices, healthcare personnel awareness

INTRODUCTION

In the provision of healthcare services, despite all kinds of precautions and interventions in accordance with the standards, complications that will inevitably occur can be encountered. The complications arising from the complications cannot be attributed to the physician and therefore there is no legal liability (1). However, some complications that are not noticed on time and cannot be taken adequate precautions can turn into medical errors. Medical errors occur due to physicians' misdiagnosis and treatment approaches, professional inexperience, imprudence, negligence, misuse of equipment, lack of attention or care, or lack of information, technical equipment and communication (2). These mistakes put the health and safety of the patients at risk and may lead to prolongation of the recovery period (3). Despite the lack of personnel, the excess number of patients, fatigue and stress due to the length of the working period, problems in the distribution of duties and powers, lack of education and motivation also play an important role in the emergence of these errors (4).

Not all medical errors are harmful to the patient. In medical malpractice, although it is predictable and preventable, it is possible to harm the patient because it is not done by the healthcare worker, and in return, punitive/legal sanctions are imposed (5). In addition, a result that is accepted as a complication by the physician may be perceived as malpractice by the patient and their relatives. In short, while every malpractice is a medical error, not every medical error is a malpractice (6).

The increase in malpractice cases in recent years has adversely affected the performance of healthcare professionals, as well as leading to defensive medicine practices with defense psychology (7). The concept of defensive medicine is defined as the healthcare professionals

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who want to be protected from malpractice accusation, resort to non-standard procedures without considering the benefit of the patient due to fears such as complaints/ disciplinary punishment/being sued/being subjected to violence, or referring patients at risk of complications to another physician/institution (8). The degree of defensive medicine is directly proportional to the malpractice risk level. Some physicians use defensive medicine deliberately, while others do it without realizing it (9).

It is possible to examine defensive medicine in two subgroups as positive and negative applications. Positive defensive medicine is physicians' requesting additional tests, examinations and consultations without medical value with the motive of preventing negligence and protecting their reputation, prescribing unnecessary medications, making detailed explanations, keeping detailed records or hospitalizing more than necessary (7). In short, it is possible to provide extra health services beyond the need (10). The main reason for applying positive defensive medicine is the desire of the physician to convince the patients that he fulfills the standards of care during the procedures, and to prove on legal grounds that the regulations and procedures are not left incomplete, on the contrary, the extra application is made. In addition to risking the safety of patients, this may also cause side effects (11).

Negative defensive medicine is avoiding procedures that will benefit the patient for fear of malpractice, avoiding patients with high risk of complications and litigation, refusing them or referring them unnecessarily (7). As a result of the deprivation of health services, there may be a risk of chronic illness, disability or death. The main reason for applying negative defensive medicine is that the physician wants to avoid legal sanctions that may arise by discarding his responsibility (12). While the common point of defensive medicine practices is to be protected from malpractice cases, negative defensive medicine, whose prevalence has increased rapidly recently, although it is not as common as positive defensive medicine, is more likely to harm the patient (7,10).

Today, people who have increased awareness of patients' rights and malpractice have started to question the health services provided and demand high compensation in malpractice cases, increasing the pressure on healthcare professionals (12) and prompting physicians to worry and uneasiness (10). Press and social media's suppression of healthcare professionals plays a major role in the increase in defensive medicine practices (9). The fact that health news, which only includes patient rights, are exaggerated due to ratings or other reasons, discredits healthcare professionals in the eyes of the public. The fact that all healthcare professionals get used to news of violence, especially against physicians, negatively affects the patient-physician relationship (13).

Defensive medicine practices are not only physician sourced, but also patient, system and administrative. Considering the unfavorable conditions of the health system, insufficient attention to patient-physician communication in the education curriculum (14), inexperience of new graduates and insufficient support from the management (9), the performance criteria applied and the lack of expertise in health law (13), physicians themselves it turns towards defensive medicine applications with its protection reflex (9). As a result, physicians make unnecessary examinations or refer patients to other institutions by acting as guarantees to avoid problems. Defensive medicine practices that adversely affect the efficiency and quality of healthcare services put patients at risk and cause unnecessary cost increases. These non-standard practices impose a macro or micro burden on the national economy (15).

MATERIAL AND METHOD

Participants were informed about the purpose of the study and their consent was obtained by paying attention to the voluntary principle. It has also been ensured that the information about the participants is kept confidential. The study was Approval for the study was given by the Ethics Committee of Dicle University Faculty of Dentistry (Date: 26.06.2019, Decision No: 2019/29-2). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

In our study, a total of 175 dentists working in Dicle University Faculty of Dentistry and Diyarbakir Oral and Dental Health Hospital and affiliated centers and determined by random sampling method were included. The relationship of defensive medicine practices performed by dentists with general characteristics such as age, physician (service) duration, gender, institution, title and specialty, if any, are examined. It is hoped that our research will contribute to the literature with different samples and findings.

Evaluation of Questionnaire

In our study, in which the volunteering principle of the physicians participating in the study was taken into consideration, the questionnaire, which is one of the quantitative data collection techniques, was used. The questionnaire, which is prepared by four academicians who are competent in their field and includes thirty-one questions in total, consists of two parts. The first part consists of six descriptive questions about the dentists who participated in the study. These questions regarding the age, duration of dentistry, gender, institution, title and specialty of dentists, if any, are shown in **Table 1**.

Table 1. Descriptive questions about dentists

Item No	Questions	Responses	n	(%)
1	How old are you?	25 years and under	6	(3.4%)
		26 to 40 years old	125	(71.4%)
		41 to 55 years old	42	(24%)
		56 years and older	2	(1.1%)
2	How many years are you a physician?	1-5 years	64	(36.6%)
		6-10 years	45	(25.7%)
		11-15 years	21	(12%)
		16-20 years	12	(6.9%)
		21 years and above	33	(18.9%)
3	Your gender?	Male	60	(34.3%)
		Female	115	(65.7%)
4	Which health institution do you work in?	Oral and dental health center	73	(41.7%)
		University Hospital	102	(58.3%)
5	What is your job title?	General practitioner	63	(36%)
		Specialist physician	14	(8%)
		Residency student	72	(41.1%)
		Faculty Member	26	(14.9%)
6	If yes, what is your area of expertise?	Oral diagnosis and radiology	4	(2.3%)
		Oral and Maxillofacial Surgery	11	(6.3%)
		Orthodontics	8	(4.6%)
		Restorative Dentistry	21	(12%)
		Pediatric Dentistry	25	(14.3%)
		Periodontology	10	(5.7%)
		Prosthodontics	23	(13.1%)
		Endodontics	8	(4.6%)
		I do not have expertise	65	(37.1%)

The second part consists of twenty-five questions aimed at determining the level of knowledge and attitude of dentists about the concept of defensive medicine (**Table 2**).

Statistical analysis

While the data were analyzed statistically, a frequency distribution table was created for general characteristics. Chi-square Test was applied to compare the answers given to the questions with categorical data and general characteristics, which are categorical variables. A confidence interval of 95% was applied. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

"Have you heard of the concept of defensive medicine (recessive medicine) before?" and "Do you ever prescribe extra medication to protect yourself from medical malpractice claims?" When the answers given by the participants to the question were analyzed, the difference between the individuals in terms of duration of practice, institution and title categories was found to be statistically significant ($p<0.05$). (**Tables 3** and **4**).

Table 3. "Have you heard of the concept of defensive medicine (recessive medicine) before?" Answers to the question

Questions	General Features		I heard	I did not hear	X2	p
Have you heard of the concept of defensive medicine (recessive medicine) before?	Age				6.874	0.076
		25 years and under	0 (0%)	6 (100%)		
		26 to 40 years old	40 (32%)	85 (68%)		
		41 to 55 years old	20 (47.6%)	22 (52.4%)		
		56 years and older	1 (50%)	1 (50%)		
	Duration of Medicine				18.679	0.001
		1-5 years	10 (15.6%)	54 (84.4%)		
		6-10 years	17 (37.8%)	28 (62.2%)		
		11-15 years	11 (52.4%)	10 (47.6%)		
		16-20 years	6 (50%)	6 (50%)		
		21 years and above	17 (51.5%)	16 (48.5%)		
	Gender				0.093	0.760
		Male	20 (33.3%)	40 (66.7%)		
		Female	41 (35.7%)	74 (64.3%)		
	Institution				5.907	0.015
		Oral and dental health center	33 (45.2%)	40 (54.8%)		
		University Hospital	28 (27.5%)	74 (72.5%)		
	Title				19.408	0.000
		General practitioner	28 (44.4%)	35 (55.6%)		
		Specialist physician	6 (42.9%)	8 (57.1%)		
		Residency student	12 (16.7%)	60 (83.3%)		
		Faculty Member	15 (57.7%)	11 (42.3%)		
	Expertise				10.083	0.259
		Oral diagnosis and radiology	0 (0%)	4 (100%)		
		Oral and Maxillofacial Surgery	5 (45.5%)	6 (54.5%)		
		Orthodontics	2 (25%)	6 (75%)		
		Restorative Dentistry	8 (38.1%)	13 (61.9%)		
		Pediatric Dentistry	6 (24%)	19 (76%)		
		Periodontology	1 (10%)	9 (90%)		
		Prosthodontics	7 (30.4%)	16 (69.6%)		
		Endodontics	4 (50%)	4 (50%)		
		I do not have expertise	28 (43.1%)	37 (56.9%)		

Table 2. Level of knowledge and attitude of dentists about the concept of defensive medicine

Item No	QUESTIONS	RESPONSES	n	(%)
7	Have you heard of the concept of defensive medicine (recessive medicine) before?	I heard	61	(34.9%)
		I did not hear	114	(65.1%)
8	Do you know enough about the concept of defensive medicine practices?	Definitely yes	5	(2.9%)
		Yes	14	(8%)
		I am indecisive	30	(17.1%)
		No	91	(52%)
		Definitely no	35	(20%)
9	Do you believe there is an increase in the number of medical malpractice cases?	Definitely yes	62	(35.4%)
		Yes	96	(54.9%)
		I am indecisive	11	(6.3%)
		No	6	(3.4%)
		Definitely no	0	(0%)
10	Will the medical malpractice case to be filed against you reduce your physician performance?	Definitely yes	46	(26.3%)
		Yes	86	(49.1%)
		I am indecisive	32	(18.3%)
		No	9	(5.1%)
		Definitely no	2	(1.1%)
11	Have you ever been sued for the alleged medical fault?	Never happened	165	(94.3%)
		Once	10	(5.7%)
		Twice	0	(0%)
		Three times	0	(0%)
		More than three	0	(0%)
12	Do you ever prescribe extra medication to protect yourself from medical malpractice claims?	Always	0	(0%)
		Most of the time	11	(6.3%)
		Sometimes	44	(25.1%)
		Rarely	35	(20%)
		Never	85	(48.6%)
13	To protect yourself from medical malpractice claims, do you ever avoid patients who are likely to sue?	Always	10	(5.7%)
		Most of the time	30	(17.1%)
		Sometimes	63	(36%)
		Rarely	44	(25.1%)
		Never	28	(16%)
14	Do you ever ask for extra consultation to protect yourself from medical malpractice claims?	Always	10	(5.7%)
		Most of the time	67	(38.3%)
		Sometimes	54	(30.9%)
		Rarely	28	(16%)
		Never	16	(9.1%)
15	Do you ever take any procedure without indications to protect yourself from medical malpractice claims?	Always	0	(0%)
		Most of the time	5	(2.9%)
		Sometimes	13	(7.4%)
		Rarely	34	(19.4%)
		Never	123	(70.3%)
16	To protect yourself from medical malpractice claims, do you ever avoid patients with complex medical problems?	Always	3	(1.7%)
		Most of the time	27	(15.4%)
		Sometimes	61	(34.9%)
		Rarely	51	(29.1%)
		Never	33	(18.9%)
17	Do you use imaging studies more often to protect yourself from medical malpractice claims?	Always	30	(17.1%)
		Most of the time	94	(53.7%)
		Sometimes	28	(16%)
		Rarely	11	(6.3%)
		Never	12	(6.9%)
18	Do you ever explain medical practices in more detail to protect yourself from medical malpractice claims?	Always	52	(29.7%)
		Most of the time	91	(52%)
		Sometimes	22	(12.6%)
		Rarely	6	(3.4%)
		Never	4	(2.3%)
19	Do you ever avoid high-complication treatments to protect yourself from medical malpractice claims?	Always	4	(2.3%)
		Most of the time	45	(25.7%)
		Sometimes	70	(40%)
		Rarely	35	(20%)
		Never	21	(12%)
20	Do you ever keep records in more detail to protect yourself from medical malpractice claims?	Always	41	(23.4%)
		Most of the time	88	(50.3%)
		Sometimes	28	(16%)
		Rarely	13	(7.4%)
		Never	5	(2.9%)
21	Do you ever place more emphasis on informed consent forms to protect yourself from medical malpractice claims?	Always	69	(39.4%)
		Most of the time	74	(42.3%)
		Sometimes	25	(14.3%)
		Rarely	7	(4%)
		Never	0	(0%)
22	In order to protect yourself from medical malpractice claims, do you refer patients at risk even though you have treatment?	Always	4	(2.3%)
		Most of the time	22	(12.6%)
		Sometimes	55	(31.4%)
		Rarely	46	(26.3%)
		Never	48	(27.4%)
23	What is your risk of facing a medical malpractice case at any time, depending on your circumstances?	Extremely high	31	(17.7%)
		Very high	36	(20.6%)
		High	63	(36%)
		Not very high	40	(22.9%)
		Not high at all	5	(2.9%)

24	Are you taking out a medical malpractice insurance policy?	I have never done	14	(8%)
		I have been doing it for the last year	45	(25.7%)
		I have been doing it for the last two years	21	(12%)
		I have been doing it for the last three years	14	(8%)
		I have been doing it for the last four years	72	(41.1%)
		I had it before, now I don't have insurance	9	(5.1%)
25	Did you feel uneasy in your practice after the new " Turkish Penal Code " came into force on June 1, 2005 (deprivation of practice of profession and art for up to three years, to be imposed upon the completion of the actual punishment for physicians even in their minor negligence)?	Definitely yes	47	(26.9%)
		Yes	67	(38.3%)
		I am indecisive	37	(21.1%)
		No	23	(13.1%)
		Definitely no	1	(0.6%)
26	Do you think a document stating "I accept all medical interventions to be made, I will not sue my doctor in case of damage" relieves the physician from responsibility?	Definitely yes	5	(2.9%)
		Yes	29	(16.6%)
		I am indecisive	48	(27.4%)
		No	74	(42.3%)
		Definitely no	19	(10.9%)
27	Have you read the "patient rights regulation" published in the official newspaper?	I've never heard of	37	(21.1%)
		I've heard, I've never read	64	(36.6%)
		I partially read	58	(33.1%)
		I read all of it	16	(9.1%)
28	Do you think that the distinction between complications and malpractice cannot be made clearly?	Definitely yes	64	(36.6%)
		Yes	79	(45.1%)
		I am indecisive	17	(9.7%)
		No	13	(7.4%)
		Definitely no	2	(1.1%)
29	Would having " medical malpractice insurance " make your medical practices more comfortable?	Definitely yes	11	(6.3%)
		Yes	67	(38.3%)
		I am indecisive	59	(33.7%)
		No	32	(18.3%)
		Definitely no	6	(3.4%)
30	Are you worried about making medical mistakes?	Always	34	(19.4%)
		Most of the time	41	(23.4%)
		Sometimes	73	(41.7%)
		Rarely	24	(13.7%)
		Never	3	(1.7%)
31	Do you use defensive medicine to protect patients and their relatives from verbal and physical violence?	Always	8	(4.6%)
		Most of the time	32	(18.3%)
		Sometimes	72	(41.1%)
		Rarely	43	(24.6%)
		Never	20	(11.4%)

Table 4. "Do you ever prescribe extra medication to protect yourself from medical malpractice claims?" Answers to the question

Questions	General Features	Always	Most of the time	Sometimes	Rarely	Never	X2	p
Do you ever prescribe extra medication to protect yourself from medical malpractice claims?	Age						7.573	0.578
	25 years and under	0 (0%)	0 (0%)	3 (50%)	1 (16.7%)	2 (33.3%)		
	26 to 40 years old	0 (0%)	9 (7.2%)	30 (24%)	29 (23.2%)	57 (45,6%)		
	41 to 55 years old	0 (0%)	2 (4.8%)	11 (26.2%)	5 (11.9%)	24 (57.1%)		
	56 years and older	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)		
	Duration of Medicine						30.021	0.003
	1-5 years	0 (0%)	2 (3.1%)	17 (26.6%)	20 (31.3%)	25 (39.1%)		
	6-10 years	0 (0%)	1 (2.2%)	13 (28.9%)	9 (20%)	22 (48.9%)		
	11-15 years	0 (0%)	5 (23.8%)	4 (19%)	1 (4.8%)	11 (52.4%)		
	16-20 years	0 (0%)	2 (16.7%)	4 (33.3%)	2 (16.7%)	4 (33.3%)		
	21 years and above	0 (0%)	1 (3%)	6 (18.2%)	3 (9.1%)	23 (69.7%)		
	Gender						5.730	0.125
	Male	0 (0%)	1 (1.7%)	20 (33.3%)	11 (18.3%)	28 (46.7%)		
	Female	0 (0%)	10 (8.7%)	24 (20.9%)	24 (20.9%)	57 (49.6%)		
	Institution						12.020	0.007
	Oral and dental health center	0 (0%)	8 (11%)	25 (34.2%)	11 (15.1%)	29 (39.7%)		
	University Hospital	0 (0%)	3 (2.9%)	19 (18.6%)	24 (23.5%)	56 (54.9%)		
	Title						26.001	0.002
	General practitioner	0 (0%)	8 (12.7%)	20 (31.7%)	9 (14.3%)	26 (41.3%)		
	Specialist physician	0 (0%)	0 (0%)	6 (42.9%)	4 (28.6%)	4 (28.6%)		
	Residency student	0 (0%)	2 (2.8%)	16 (22.2%)	20 (27.8%)	34 (47.2%)		
	Faculty Member	0 (0%)	1 (3.8%)	2 (7.7%)	2 (7.7%)	21 (80.8%)		
	Expertise						26.748	0.316
	Oral diagnosis and radiology	0 (0%)	0 (0%)	0 (0%)	2 (50%)	2 (50%)		
	Oral and Maxillofacial Surgery	0 (0%)	1 (9.1%)	2 (18.2%)	3 (27.3%)	5 (45.5%)		
	Orthodontics	0 (0%)	0 (0%)	1 (12.5%)	1 (12.5%)	6 (75%)		
	Restorative Dentistry	0 (0%)	0 (0%)	4 (19%)	2 (9.5%)	15 (71.4%)		
	Pediatric Dentistry	0 (0%)	2 (8%)	8 (32%)	7 (28%)	8 (32%)		
	Periodontology	0 (0%)	0 (0%)	2 (20%)	2 (20%)	6 (60%)		
	Prosthodontics	0 (0%)	0 (0%)	4 (17.4%)	5 (21.7%)	14 (60.9%)		
	Endodontics	0 (0%)	0 (0%)	3 (37.5%)	3 (37.5%)	2 (25%)		
	I do not have expertise	0 (0%)	8 (12.3%)	20 (30.8%)	10 (15.4%)	27 (41.5%)		

"Do you know enough about the concept of defensive medicine practices?", "Do you have a medical malpractice insurance policy?" and "Are you worried about making medical mistakes?" When the answers given by the participants to the question were analyzed, the difference between individuals in age, duration of practice and title categories was found to be statistically significant (p<0.05).

"Do you believe there is an increase in the number of medical malpractice cases?" and "Do you ever avoid patients who are likely to sue, in order to protect yourself from medical malpractice claims?" When their answers to the question were analyzed, the difference between individuals in the category of the institution they worked at was found to be statistically significant (p<0.05).

"Will the medical malpractice case filed against you decrease your physician performance?" When the answers given by the participants to the question were analyzed, it was found that the difference between individuals in terms of duration of practice and the categories of the institution worked was statistically significant (p<0.05).

The participants were asked "Do you ever avoid treatments with high complications in order to protect yourself from medical malpractice claims?" When their answers to the question were analyzed, the difference between individuals in the age category was found to be statistically significant (p<0.05) (**Table 5**).

"To protect yourself from medical malpractice claims, do you ever refer patients at risk even though you have treatment?" When the answers given by the participants to the question were analyzed, the difference between individuals in the institution and title categories was found to be statistically significant (p<0.05) (**Table 6**).

"Have you ever been sued for medical malpractice?", "Do you pay more attention to informed consent forms in order to protect yourself from medical malpractice claims?" , "Do you think that the distinction between complications and malpractice cannot be made clearly?" and "Do you use defensive medicine to protect patients and their relatives from verbal and physical violence?" When the answers given by the participants to the questions were analyzed, the difference between individuals in the specialty category was found to be statistically significant (p<0.05) (**Table 7**).

Table 5. "Do you ever avoid treatments with high complications in order to protect yourself from medical malpractice claims?" Answers to the question

Questions	General Features	Always	Most of the time	Sometimes	Rarely	Never	X2	p
Do you ever avoid high-complication treatments to protect yourself from medical malpractice claims?	Age						22.239	0.035
	25 years and under	0 (0%)	0 (0%)	1 (16.7%)	5 (83.3%)	0 (0%)		
	26 to 40 years old	3 (2.4%)	38 (30.4%)	48 (38.4%)	22 (17.6%)	14 (11.2%)		
	41 to 55 years old	1 (2.4%)	7 (16.7%)	19 (45.2%)	8 (19%)	7 (16.7%)		
	56 years and older	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)		
	Duration of Medicine						15.963	0.456
	1-5 years	1 (1.6%)	18 (28.1%)	21 (32.8%)	19 (29.7%)	5 (7.8%)		
	6-10 years	1 (2.2%)	15 (33.3%)	19 (42.2%)	6 (13.3%)	4 (8.9%)		
	11-15 years	1 (4.8%)	5 (23.8%)	9 (42.9%)	2 (9.5%)	4 (19%)		
	16-20 years	0 (0%)	2 (16.7%)	7 (58.3%)	2 (16.7%)	1 (8.3%)		
	21 years and above	1 (3%)	5 (15.2%)	14 (42.4%)	6 (18.2%)	7 (21.2%)		
	Gender						1.568	0.815
	Male	1 (1.7%)	14 (23.3%)	23 (38.3%)	15 (25%)	7 (11.7%)		
	Female	3 (2.6%)	31 (27%)	47 (40.9%)	20 (17.4%)	14 (12.2%)		
	Institution						4.806	0.308
	Oral and dental health center	3 (4.1%)	19 (26%)	33 (45.2%)	11 (15.1%)	7 (9.6%)		
	University Hospital	1 (1%)	26 (25.5%)	37 (36.3%)	24 (23.5%)	14 (13.7%)		
	Title						9.205	0.685
	General practitioner	3 (4.8%)	18 (28.6%)	28 (44.4%)	8 (12.7%)	6 (9.5%)		
	Specialist physician	0 (0%)	3 (21.4%)	6 (42.9%)	3 (21.4%)	2 (14.3%)		
	Residency student	1 (1.4%)	19 (26.4%)	25 (34.7%)	19 (26.4%)	8 (11.1%)		
	Faculty Member	0 (0%)	5 (19.2%)	11 (42.3%)	5 (19.2%)	5 (19.2%)		
	Expertise						45.924	0.053
	Oral diagnosis and radiology	0 (0%)	2 (50%)	0 (0%)	0 (0%)	2 (50%)		
	Oral and Maxillofacial Surgery	0 (0%)	6 (54.5%)	0 (0%)	2 (18.2%)	3 (27.3%)		
	Orthodontics	1 (12.5%)	4 (50%)	2 (25%)	1 (12.5%)	0 (0%)		
	Restorative Dentistry	0 (0%)	2 (9.5%)	7 (33.3%)	8 (38.1%)	4 (19%)		
	Pediatric Dentistry	0 (0%)	5 (20%)	12 (48%)	7 (28%)	1 (4%)		
	Periodontology	0 (0%)	2 (20%)	6 (60%)	2 (20%)	0 (0%)		
	Prosthodontics	0 (0%)	5 (21.7%)	9 (39.1%)	6 (26.1%)	3 (13%)		
	Endodontics	0 (0%)	1 (12.5%)	5 (62.5%)	1 (12.5%)	1 (12.5%)		
	I do not have expertise	3 (4.6%)	18 (27.7%)	29 (44.6%)	8 (12.3%)	7 (10.8%)		

Table 6. "In order to protect yourself from medical malpractice allegations, do you refer patients at risk even though you have treatment?" Answers to the question

Questions	General Features	Always	Most of the time	Sometimes	Rarely	Never	X2	p
In order to protect yourself from medical malpractice claims, do you refer patients at risk even though you have treatment?	Age						9.424	0.666
	25 years and under	0 (0%)	0 (0%)	2 (33.3%)	2 (33.3%)	2 (33.3%)		
	26 to 40 years old	3 (2.4%)	17 (13.6%)	43 (34.4%)	31 (24.8%)	31 (24.8%)		
	41 to 55 years old	1 (2.4%)	5 (11.9%)	10 (23.8%)	11 (26.2%)	15 (35.7%)		
	56 years and older	0 (0%)	0 (0%)	0 (0%)	2 (100%)	0 (0%)		
	Duration of Medicine						15.184	0.511
	1-5 years	2 (3.1%)	5 (7.8%)	24 (37.5%)	15 (23.4%)	18 (28.1%)		
	6-10 years	1 (2.2%)	7 (15.6%)	13 (28.9%)	14 (31.1%)	10 (22.2%)		
	11-15 years	0 (0%)	5 (23.8%)	8 (38.1%)	3 (14.3%)	5 (23.8%)		
	16-20 years	0 (0%)	3 (25%)	4 (33.3%)	2 (16.7%)	3 (25%)		
	21 years and above	1 (3%)	2 (6.1%)	6 (18.2%)	12 (36.4%)	12 (36.4%)		
	Gender						3.676	0.452
	Male	3 (5%)	8 (13.3%)	16 (26.7%)	16 (26.7%)	17 (28.3%)		
	Female	1 (0.9%)	14 (12.2%)	39 (33.9%)	30 (26.1%)	31 (27%)		
	Institution						22.492	0.000
	Oral and dental health center	1 (1.4%)	15 (20.5%)	31 (42.5%)	17 (23.3%)	9 (12.3%)		
	University Hospital	3 (2.9%)	7 (6.9%)	24 (23.5%)	29 (28.4%)	39 (38.2%)		
	Title						34.479	0.001
	General practitioner	1 (1.6%)	14 (22.2%)	26 (41.3%)	15 (23.8%)	7 (11.1%)		
	Specialist physician	0 (0%)	1 (7.1%)	8 (57.1%)	2 (14.3%)	3 (21.4%)		
	Residency student	3 (4.2%)	7 (9.7%)	17 (23.6%)	21 (29.2%)	24 (33.3%)		
	Faculty Member	0 (0%)	0 (0%)	4 (15.4%)	8 (30.8%)	14 (53.8%)		
	Expertise						42.587	0.100
	Oral diagnosis and radiology	0 (0%)	0 (0%)	1 (25%)	1 (25%)	2 (50%)		
	Oral and Maxillofacial Surgery	0 (0%)	2 (18.2%)	3 (27.3%)	1 (9.1%)	5 (45.5%)		
	Orthodontics	1 (12.5%)	0 (0%)	1 (12.5%)	3 (37.5%)	3 (37.5%)		
	Restorative Dentistry	0 (0%)	2 (9.5%)	9 (42.9%)	4 (19%)	6 (28.6%)		
	Pediatric Dentistry	0 (0%)	3 (12.0%)	7 (28%)	9 (36%)	6 (24%)		
	Periodontology	0 (0%)	0 (0%)	1 (10%)	4 (40%)	5 (50%)		
	Prosthodontics	2 (8.7%)	0 (0%)	5 (21.7%)	7 (30.4%)	9 (39.1%)		
	Endodontics	0 (0%)	1 (12.5%)	2 (25%)	1 (12.5%)	4 (50%)		
	I do not have expertise	1 (1.5%)	14 (21.5%)	26 (40%)	16 (24.6%)	8 (123%)		

Table 7. "Do you use defensive medicine to protect patients and their relatives from verbal and physical violence?" Answers to the question

Questions	General Features	Definitely Yes	Yes	I am indecisive	No	Definitely No	X2	p
Do you use defensive medicine to protect patients and their relatives from verbal and physical violence?	Age						10.740	0.551
	25 years and under	0 (0%)	3 (50%)	1 (16.7%)	2 (33.3%)	0 (0%)		
	26 to 40 years old	6 (4.8%)	22 (17.6%)	55 (44%)	29 (23.2%)	13 (10.4%)		
	41 to 55 years old	2 (4.8%)	7 (16.7%)	16 (38.1%)	11 (26.2%)	6 (14.3%)		
	56 years and older	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)		
	Duration of Medicine						17.174	0.374
	1-5 years	4 (6.3%)	11 (17.2%)	26 (40.6%)	17 (26.6%)	6 (9.4%)		
	6-10 years	1 (2.2%)	8 (17.8%)	24 (53.3%)	10 (22.2%)	2 (4.4%)		
	11-15 years	2 (9.5%)	6 (28.6%)	6 (28.6%)	2 (9.5%)	5 (23.8%)		
	16-20 years	0 (0%)	3 (25%)	4 (33.3%)	4 (33.3%)	1 (8.3%)		
	21 years and above	1 (3%)	4 (12.1%)	12 (36.4%)	10 (30.3%)	6 (18.2%)		
	Gender						1.398	0.844
	Male	3 (5%)	11 (18.3%)	24 (40%)	13 (21.7%)	9 (15%)		
	Female	5 (4.3%)	21 (18.3%)	48 (41.7%)	30 (26.1%)	11 (9.6%)		
	Institution						5.762	0.218
	Oral and dental health center	4 (5.5%)	18 (24.7%)	31 (42.5%)	13 (17.8%)	7 (9.6%)		
	University Hospital	4 (3.9%)	14 (13.7%)	41 (40.2%)	30 (29.4%)	13 (12.7%)		
	Title						19.811	0.071
	General practitioner	4 (6.3%)	16 (25.4%)	28 (44.4%)	10 (15.9%)	5 (7.9%)		
	Specialist physician	0 (0%)	2 (14.3%)	5 (35.7%)	4 (28.6%)	3 (21.4%)		
	Residency student	3 (4.2%)	14 (19.4%)	29 (40.3%)	21 (29.2%)	5 (6.9%)		
	Faculty Member	1 (3.8%)	0 (0%)	10 (38.5%)	8 (30.8%)	7 (26.9%)		
	Expertise						48.467	0.031
	Oral diagnosis and radiology	0 (0%)	0 (0%)	2 (50%)	1 (25%)	1 (25%)		
	Oral and Maxillofacial Surgery	0 (0%)	2 (18.2%)	6 (54.5%)	3 (27.3%)	0 (0%)		
	Orthodontics	2 (25%)	3 (37.5%)	2 (25%)	1 (12.5%)	0 (0%)		
	Restorative Dentistry	0 (0%)	4 (19%)	8 (38.1%)	8 (38.1%)	1 (4.8%)		
	Pediatric Dentistry	1 (4%)	2 (8%)	10 (40%)	10 (40%)	2 (8%)		
	Periodontology	1 (10%)	1 (10%)	5 (50%)	3 (30%)	0 (0%)		
	Prosthodontics	0 (0%)	3 (13%)	6 (26.1%)	5 (21.7%)	9 (39.1%)		
	Endodontics	0 (0%)	1 (12.5%)	5 (62.5%)	1 (12.5%)	1 (12.5%)		
	I do not have expertise	4 (6.2%)	16 (24.6%)	28 (43.1%)	11 (16.9%)	6 (9.2%)		

"Do you ever ask for extra consultation to protect yourself from medical malpractice claims?" When the answers given by the participants to the question were analyzed, the difference between individuals in age, duration of practice and gender categories was found to be statistically significant ($p<0.05$).

"Do you ever take any procedure without indications to protect yourself from medical malpractice claims?" When the answers given by the participants to the question were analyzed, the difference between individuals in the gender category was found to be statistically significant ($p<0.05$).

"Did you feel uneasy in your medical practice after the new Turkish penal code came into force on 1 June 2005 (the penalty of deprivation of practice of profession and art for up to three years, to be applied to physicians after the completion of the actual punishment, even in the slightest negligence)?" When the answers given by the participants to the question were analyzed, the difference between the individuals in terms of duration of medicine, title and field of specialty was found to be statistically significant ($p<0.05$).

"Have you read the patient rights regulation published in the official newspaper?" When the answers given by the participants to the question were analyzed, the difference between individuals in all categories was found to be statistically significant ($p<0.05$).

"Does taking medical malpractice insurance make your medical practices more comfortable?" When the answers given by the participants to the question were analyzed, it was found that the difference between individuals in age, duration of practice, institution and title categories was statistically significant ($p<0.05$).

"To protect yourself from medical malpractice claims, do you ever avoid patients with complex medical problems?", "Do you use imaging tests more frequently to protect yourself from medical malpractice claims?" Do you ever keep records in more detail to protect yourself from medical malpractice claims? and "Do you think" I accept all medical interventions, I will not sue my physician when the damage occurs "" would a document relieve the physician from responsibility? " When the answers given by the participants to the questions were analyzed, the difference between individuals in any category was not found to be statistically significant ($p>0.05$).

DISCUSSION

In recent years, many researches have been conducted on examining the reasons for defensive medicine practice and reducing its effectiveness in order to increase the quality and efficiency of healthcare services. Studies have shown that healthcare professionals tend to practice positive and negative defensive medicine as a result of a medical error, due to the fear of being subjected to violence, complaints or litigation, fear of protecting their reputation, or pressures based on the business environment and media (8).

Johnston (14) claimed that medical school students were directed to defensive medicine during their education. In a study conducted by O'Leary et al. (16), It was determined that 96% of the assistant physicians and 34% of the 4th grade students of the Faculty of Medicine had applied to positive defensive medicine at least once in the past. In a study involving 100 specialist physicians, Motta et al. stated that 50% of the doctors were leaning towards the practice of defensive medicine due to legal concerns (17). In our study, the rate of those who answered "I am indecisive" to the question "Do you use defensive medicine to protect against verbal and physical violence by patients and their relatives?" was higher than those who answered "yes" or "no" in many categories.

Studies have shown that physicians do not have enough information about possible future malpractice litigation processes. Arikan et al. (18) reported that the knowledge level of the newcomers to the medical profession is less than the experienced ones. In a study conducted in our country, it was stated that approximately 58% of the physicians were not aware of malpractice procedures (19).

In our study, 32% of the physicians in the 26-40 age group, who constitute the vast majority (71.4%) of the participants, stated that they were not aware of the concept of defensive medicine. It was understood that only 10.85% of them had knowledge about the content of the malpractice concept. 84.4% of those with 1-5 years of medical experience, 36.6% of the participants, and 83.3% of the specialty students with the largest share, with 41.1%, emphasized that they do not know this concept at all. Among those who have partially or completely read the patient rights regulation published in the official newspaper, those who have a medical service period of 21 years or more (69.7%) take the lead.

Yildirim et al. (20) concluded in a study involving 125 physicians that 69.7% of the doctors practiced defensive medicine. Bishop et al. (21) emphasized that 91% of the physicians acted defensively in a study in which 1231 doctors participated. Ozata et al. (22), in their study in which 173 physicians participated, concluded that approximately 93% of the doctors used defensive medicine in the past. In a study conducted on 117 gynecologists, Ali et al. (23) found that approximately 41% of the physicians used positive and 31% negative defensive medicine. In a similar study, it was found that 98% of the research assistants

working at Dicle University Medical Faculty Hospital were practicing positive and 92% negative defensive medicine (24). In a study conducted among family physicians in Izmir, it was reported that 100% of physicians practiced defensive medicine (25), and in another study conducted on dentists, this rate was 93.9% (26).

In a study conducted on 229 physicians, Ozata et al. (27) stated that male physicians were more afraid of high-risk patients, while Moosazadeh et al. (15) reported that female physicians mostly turned to negative defensive medicine. Solaroglu et al. (28) concluded that there is no significant relationship between the rate of defensive medicine application and gender.

In our study conducted on 175 dentists, the rate of being anxious about medical mistakes was found to be equally high in men and women (98.3%). Physicians under 25 years of age (100%) and doctors with 1-5 years of experience (98.4%) are the leading ones who are worried about making medical mistakes. Oral and Maxillofacial Diseases and Surgery (81.8%) and Pedodontics (80%) are the leading areas of uneasiness after the enactment of the new Turkish Penal Code dated June 1, 2005. Most of the physicians in almost all categories think that the complication-malpractice distinction cannot be made clearly. Only 5.71% of the participants in the study stated that a malpractice lawsuit was filed against them before, and only a very small portion (6.28%) stated that the malpractice lawsuit to be filed against them would not affect their physician performance.

In our study, it was observed that male (86.7%) and female (82.6%) participants avoided similar rates of patients with a high probability of filing a malpractice case. While the rate of physicians working in the Oral and Dental Health Center to avoid patients with high probability of filing malpractice cases is 93.2%, this rate is 77.5% for those working at the University Hospital. While 45% of male physicians can perform procedures without indication to avoid malpractice claim, it has been determined that this rate is 21.7% for female participants. Periodontology (90%) and Orthodontics (87.5%) physicians were the leading specialists who avoided performing unindicated procedures for the purpose of defensive medicine.

Consistent with these findings, the participants explained the medical practices for positive defensive medicine to their patients in more detail (96.7% for men, 98.3% for women and 90.9% for Oral and Maxillofacial Surgeons who needed detailed explanation), they gave more importance to informed consent forms (95% in men, 96.5% in women, 100% in physicians with 16-20 years of experience and 96.15% in faculty members) and they kept the records more detailed (93.3% in men, 99.1% in women, while those who kept the records less detailed Endodontics doctors 87.5%). 90.28% of the participants agreed that there has been an increase in the number of malpractice cases in recent years. We are of the opinion that the high rates are due to the fear of high compensation for malpractice cases, which have increased recently, or the fear of physicians being subjected to administrative penalties.

In a study conducted with the participation of 307 physicians, Catino (8) reported that young physicians were more inclined to practice defensive medicine. In a study conducted on 425 physicians, Akinci et al. (29) reported that inexperienced physicians avoided patients inclined to sue, and the rate of requesting more examinations decreased following the increase in experience. In a study conducted on 204 doctors with different specialties, Ortashi et al. (30) stated that 78% of the participants applied defensive medicine by making unnecessary examinations or referring patients to other physicians, but physicians with professional experience used this method less.

In a study conducted with the participation of 131 gastroenterologists, Hiyama et al. (11) stated that 98% of physicians used defensive medicine, 68% referred patients unnecessarily, 54% recommended unnecessary invasive procedures, 36% requested additional examinations, 16% explained that he was prescribing unnecessary medication. He stated that experienced doctors were less inclined to negative defensive medicine practices, although 75% of the participants avoided some interventional procedures and 53% avoided high-risk patients. Mete et al. (31), in their study, in which 234 physicians participated, reported that as professional experience increased, physicians were less afraid of risky patients. It was found that physicians requested less examination and consultation or applied less referral procedures. It was understood that doctors who had previously encountered malpractice cases avoided making mistakes in order not to encounter a new complaint.

In our study, it was concluded that participants with less than 16 years of medical experience required more consultations than experienced physicians to avoid malpractice claims. It was observed that the areas of expertise requiring the most consultation for the purpose of defensive medicine were Oral Diagnosis and Radiology (100%), Prosthetic Dentistry (95.7%) and Restorative Dentistry (95.2%). It has been observed that additional drug prescribing behavior decreases with increasing age (66.7% for 25 years and below vs. 42.9% for 41-55 years) and with increasing medical experience (e.g. 60.9% for 1-5 years vs. 30.3% for 21 years and over). It was determined that the specialty areas that mostly wrote extra drugs were Endodontics (75%) and Pedodontics (68%).

Studdert et al. (32) in a study conducted on 824 physicians, found that 93% of the participants had used defensive medicine in the past, 42% of them reduced the practices to be performed with risk anxiety, 59% requested additional examinations and 52% made unnecessary referrals (10). In a study involving 877 physicians, Asher et al. stated that 59% of the doctors had unnecessary examinations, 50% requested a consultation even though it was not necessary, and 24% suggested unnecessary invasive procedures.

In the study conducted by Başer et al. (25) with the participation of 81 family physicians, it was determined that 70% of the doctors practiced defensive medicine in order to avoid legal problems. It was observed that 37% of the physicians had unnecessary examinations, 61% requested a consultation even though it was not necessary, 78% prescribed unnecessary drugs, 68% made detailed explanations and approximately 94% kept detailed records. Approximately 55% of the participants admitted that they hesitated from the patients with a tendency to sue and 71% from the treatments with high risk of complications.

In our study, for the purpose of defensive medicine, those who avoided the patients with complex medical problems the most and wanted the most imaging examinations were Orthodontics and Periodontology. The branches of specialization with the lowest rate of avoiding treatments with high complications are Oral Diagnosis and Radiology (50%) and Oral and Maxillofacial Diseases and Surgery (72.7%). It was found interesting that all specialties referred at least 50% of patients at risk despite having treatment possibilities, albeit lower than those without expertise (87.7%).

Being subjected to complaints or being sued can lead to emotional reactions in healthcare professionals such as embarrassment, guilt, anger and depression. Even if the lawsuit will result in favor of the physician, it will cause loss of reputation, and professional liability insurance for such situations cannot prevent the implementation of defensive medicine practices (33). Studdert et al. (10) stated that physicians who think that malpractice insurance cannot compensate for the damage are twice as inclined to apply positive and negative defensive medicine compared to other specialist physicians.

In our study, "What is your risk of encountering a medical malpractice case at any time according to the conditions you are in?" Oral and Maxillofacial Diseases and Surgery physicians answered the question with an extremely high rate of 54.5% and a very high answer of 45.5% (total 100%). Oral Diagnosis and Radiology (75%) and Endodontics have reported that they do not see a high risk at a rate of 50%."Does taking malpractice insurance make your medical practices more comfortable?" those who give a positive answer to the question are mostly young physicians under the age of 25 (100%), those over 56 years old (100%) and those with 1-5 years of experience (64.1%).12 physicians (9.6%) in the 26-40 age group and 2 physicians (4.8%) in the 41-55 age group stated that they had never had a malpractice insurance policy, while 25% of Endodontics specialty physicians had declared that he is not. The rate of those who think that signing a document stating that patients will not sue their physician when medical damage occurs will not relieve the physician from responsibility is slightly more than half of the participants working both in the Oral and Dental Health Center and University Hospital.

In recent years, studies have come to the fore on which branches defensive medicine practices are concentrated on and how they can be prevented. Studies show that physicians complain the most among healthcare professionals of patients. Increasing malpractice cases in our country have been particularly effective in doctors preferring less risky departments when determining their specialty (34).

In the light of all these evaluations, it can be said that health services always involve risks that may lead to medical malpractice cases and these cases put a great pressure on healthcare professionals who do not have sufficient equipment. For this reason, malpractice litigation procedures should never rise to a level that discourages physicians from their profession and hurts their lives. Healthcare professionals, on the other hand, should take care to do their profession in the best possible way, not with hesitation, should know their legal responsibilities and show the necessary sensitivity.

CONCLUSION

Especially in our country, the stress experienced by healthcare professionals due to their working conditions and heavy workload plays an important role in the formation of medical errors. We believe that increasing the quality and efficiency of healthcare services can only be possible by eliminating the worries that healthcare professionals feel while performing their duties. We believe that improving working conditions and providing a peaceful and safe environment will lead to a decrease in defensive medicine practices.

Since the vast majority of physicians in our country do not have the necessary knowledge about medical errors and malpractice, regular training programs, seminars and conferences should be planned in this regard, and the experience of experienced physicians should be utilized in solving the problems. In new researches about defensive medicine applications, it would be appropriate to examine the effect of malpractice concern on the choice of specialty and the economy of our country.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was given by the Ethics Committee of Dicle University Faculty of Dentistry (Date: 26.06.2019, Decision No: 2019/29-2).

Informed Consent: All physicians signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Kuzgun U. Complication or Malpractice? TOTBID Derg 2019; 18: 98-101.
2. Kahriman İ, Ozturk H. Evaluating Medical Errors Made by Nurses During Their Diagnosis, Treatment and Care Practices. J Clin Nurs 2016; 25: 2884-94.
3. Bakir EP, Bakir S, Unal S, Uysal E. The effect of restorative dentistry practices on the vital signs of healthy individuals. J Health Sci Med 2021; 4: 434-40.
4. Flotta D, Rizza P, Bianco A, Pileggi C, Pavia M. Patient safety and medical errors: knowledge, attitudes and behavior among ıtalian hospital physicians. Int J Quality Health Care 2012; 24: 258-65.
5. Ozer O, Tastan K, Set T, Cayir Y, Sener M. Tibbi hatali uygulamalar. Dicle Tip Derg 2015; 42: 394-7.
6. Karatas M, Yakinci C. Tibbi hata nedenleri ve çözüm yolları. Inönü Üniv Tıp Fak Derg 2010; 17: 233-6.
7. Bakir EP, Bakir S, Unal S, Sonkaya E. Are healthcare professionals sufficiently aware of dental ethics? Fields research in southeast Turkey. Biotechnol Biotechnologic Equip 2021; 35: 325-33.
8. Yesiltas A. Erdem R. A qualitative study of violence and defensive medicine practices. Akademik Sosyal Arastirmalar Derg 2018; 6: 486-500.
9. Montanera D. The importance of negative defensive medicine in the effects of malpractice reform. Eur J Health Econ 2016; 17: 355-69.
10. Studdert DM, Mello MM, Sage WM, et al. Defensive medicine among high-risk specialist physicians in a volatile malpractice environment. JAMA 2005; 1: 2609-17.
11. Hiyama T, Yoshihara M, Tanaka S, et al. Defensive medicine practices among gastroenterologists in Japan. World J Gastroenterol 2006; 12: 7671-5.
12. Yilmaz K, Polat O, Kocamaz B. The legal analysis of defensive medicine acts. Turkiye Adalet Akademisi Derg 2014; 5: 19-51.
13. Toraman A, Carikci IH. The evaluation of the causes of defensive medicines with the vision of physicians. Süleyman Demirel Üniv Vizyoner Derg 2019; 10: 40-51.
14. Johnston WF, Rodriguez RM, Suarez D, Fortman J. Study of medical students' malpractice fear and defensive medicine: a "hidden curriculum?" West J Emerg Med 2014; 15: 293-8.
15. Moosazadeh M, Movahednia M, Movahednia N, Amiresmaili M, Aghaei I. Determining the frequency of defensive medicine among general practitioners in Southeast Iran. IJHPM 2014; 2: 119-23.
16. O'Leary KJ, Choi J, Watson K, Williams MV. Medical students' and residents' clinical and educational experiences with defensive medicine. Acad Med 2012; 87: 142-8.
17. Motta S, Testa D, Cesari U, Quaremba G, Motta G. Medical liability, defensive medicine and professional ınsurance ın otolaryngology. BMC Res Notes 2015; 8: 343.
18. Arikan A, Cinarli S, Aykar FS, Sayan A. Attitudes of medical malpractice in pediatric surgery. J Pediatr Res 2017; 4: 117-22.
19. Teke HY, Alkan HA, Basbulut AZ, Canturk G. Aspect of physicians and learning level to legal regulation about with malpractice: questionnaire training. Turkiye Klinikleri J Foren Med 2007; 4: 61-7.
20. Yildirim A, Aksu M, Cetin İ, Sahan AG. Knowledge of and attitudes towards malpractice among physicians in Tokat, Turkey. Cumhuriyet Med J 2009; 31: 356-66.
21. Bishop TF, Federman AD, Keyhani S. Physicians' views on defensive medicine: a national survey. Arch Intern Med 2010; 170: 1081-3.
22. Ozata M, Ozer K, Akkoca Y. Investigation of defensive medical applications of doctors who work in Konya city center. Gumushane Uni Saglık Bil Derg 2018; 7: 132-9.
23. Ali AA, Hummeida ME, Elhassan YAM, Nabag WOM, Ahmed MAA, Adam GK. Concept of defensive medicine and litigation among Sudanese doctors working in obstetrics and gynecology. BMC Medical Ethics 2016; 17: 1-5.
24. Gocen O, Yilmaz A, Aslanhan H, Celepkolu T, Tuncay S, Dirican E. Assistant physicians knowledge and attitudes about defensive medical practices, work-related stress and burnout levels. Turk J Fam Med Primary Care 2018; 12: 77- 87.
25. Baser A, Kolcu G, Cigirgil Y, Kadinkiz B, Ongel K. Evaluation of the opinions of family doctors working in Izmir Karsiyaka district on defensive medical practices. Smyrna Tip Derg 2014; 4: 16-24.
26. Baser A, Kolcu MIB, Kolcu G, Balci UG. Validity and reliability of the Turkish version of the defensive medicine behaviour scale: preliminary study. Tepecik Egit Hast Derg 2014; 24: 99-102.
27. Ozata M, Terlemez A, Ozer K, Akkoca Y. Defensive dentistry: the example of Konya, 2019; 4: 179-88.
28. Solaroglu I, Izci Y, Yeter HG, Metin MM, Keles GE. Health transformation project and defensive medicine practice among neurosurgeons in Turkey. PLoS One 2014; 9: 1-7.
29. Akinci SB, Saricaoglu F, Erden IA, Koseoglu A, Aypar U. Anesteziyologlarda defansif tıp uygulamalarının arastirilmasi. Anestezi Derg 2013; 21: 151-6.
30. Ortashi O, Virdee J, Hassan R, Mutrynowski T, Abu-Zidan, F. The practice of defensive medicine among hospital doctors in the United Kingdom. BMC Med Ethics 2013; 14: 1-6.
31. Mete B, Nacar E, Tekin C, Unver E, Gunes G. Investigating the defensive medical practices of the physicians working in the city center of Malatya. Medicine Sci Int Med J 2017; 6: 270-5.
32. Asher E, Greenberg-Dotan S, Halevy J, Glick S, Reuveni H. Defensive medicine in Israel-a nationwide survey. Plos One 2012; 7: 1-7.
33. Bernstein J. Malpractice: problems and solutions. Clin Orthop Relat Res 2013; 471: 715-20.
34. Yavuz I, Camsari UM, Arisoy Y. The impact of healthcare reform program on post-gradate-training preferences in Turkey. Turkiye Klinikleri J Med Sci 2017; 37: 53-60.

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Temperament and character traits in young men diagnosed with idiopathic scoliosis

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ABSTRACT

Introduction: The aim of this study is to examine whether the temperament and character traits of young men diagnosed with idiopathic scoliosis (IS), known as the three-dimensional deformity of the spine and trunk, which begins to emerge during the growth period and progress with changes in the quality of life in adulthood, are different from those without idiopathic scoliosis.

Material and Method: A total of 162 IS and 162 healthy male individuals were included in the study. Scoliosis level was evaluated with the Cobb method and temperament and character traits were evaluated with the Temperament and Character Inventory. The data were evaluated with SPSS ver.22.0 program and $p<0.05$ was considered significant in the analyses.

Results: In our study, no significant difference was found between the groups according to the total/subscale scores of temperament dimensions of harm avoidance, novelty seeking and reward dependence. Persistence and novelty seeking-disorderliness subscale scores were significantly lower in study group compared to the healthy control group. There was no significant difference between groups in character trait scores.

Conclusion: The findings of our study revealed that there are differences in temperament and character traits between young men with idiopathic scoliosis and the control group. More studies are needed to determine this difference in women with idiopathic scoliosis and symptomatic individuals.

Keywords: Character, idiopathic scoliosis, novelty-seeking, persistence, personality, temperament

INTRODUCTION

Idiopathic scoliosis (IS) is a three-dimensional deformity of the spine and that becomes noticeable during growth and progresses with changes in quality of life in adulthood. Diagnosis is made when the large curve of the spine (Cobb angle) is more than 10° in anteroposterior X-ray image taken while standing (1, 2). The prevalence of IS is between 0.35% and 5.2%, and its incidence in girls is three times higher than in boys during adolescence (3, 4, 5).

The cause of 85% of IS is unknown and its etiology focuses on biomechanical, neural, metabolic, hormonal changes, and genetic and environmental factors (6). Most of the cases are asymptomatic and some of them may have body shape disorders (2), neck and back pain, decreased lung capacity due to deformity level, weakness of respiratory muscles and decreased exercise capacity (7).

In adult patients, scoliosis is divided into four groups according to the configuration of the Cobb angle (8). Type I is primary degenerative scoliosis. It is mostly found in the thoracolumbar or lumbar spine. Type II is progressive idiopathic scoliosis. It is found in the thoracic, thoracolumbar and/or lumbar spine. Type III is secondary degenerative scoliosis. Type IIIa is scoliosis that occurs in the context of pelvic obliqueness following idiopathic or other types of scoliosis, or due to leg length discrepancy, hip pathology, or lumbosacral transition anomaly. It is mostly found in the thoracolumbar, lumbar, or lumbosacral spine. Type IIIb is scoliosis secondary to metabolic bone disease (mostly osteoporosis) with asymmetric arthritis disease and/or vertebral fractures.

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Body shape disorder in idiopathic scoliosis can cause psychosocial problems such as dissatisfaction with the physical appearance (7), limitations in social activities (1), problems in parent and peer relationships (9), deterioration in body image, decrease in self-esteem (10) and decrease in quality of life (11).

Body appearance in scoliosis plays an important role in personality traits and physical self-perception (12). Interesting findings have emerged in studies examining personality traits and related factors in scoliosis patients. In studies investigating the personality traits of patients with IS, it has been reported that depressiveness and neuroticism are more common in patients with scoliosis, they have lower self-esteem (13, 14, 15), they exhibit feelings of insecurity and inferiority (14), they have mild introversion and mild neurotic tendencies (16), personality disorders, and increased levels of psychotic symptoms (17). In a systematic review study, it was reported that thoughts about negative body image were associated with higher levels of neuroticism and lower levels of extraversion and conscientiousness in individuals with scoliosis (18). In addition to body appearance, treatment approaches in idiopathic scoliosis also affect personality traits. In a study (19), more self-criticism was reported in patients with IS who were treated conservatively than in healthy individuals, while more self-criticism, neuroticism, and depressiveness were reported in those who received surgical treatment.

According to Cloninger's psychobiological model, four temperament and three character dimensions explain personality traits (20, 21). Temperament dimensions consists of novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P) develop with the effect of 40-60% genetic factors, while the character dimension consisting of self-directedness (SD), cooperation (CO), and self-transcendence (ST) develops with the effect of 15-30% environmental factors and 10-15% genetic factors. The character dimension of personality includes individual differences in self-concept about personal goals and values, in contrast to the temperament dimension, which includes differences in automatic emotional responses and habits. In other words, temperament traits reflect individual differences in perceptual dispositions and skills, are genetically homogeneous, and inherited independently, while character traits mature the personality with individual and social influences they produce with age (20, 21).

Many studies have been performed on personality traits handling temperament and character dimensions in diseases related to the musculoskeletal system (22, 23, 24, 25, 26). In a study in which personality traits were investigated in 46 patients with Classical Myotonic Dystrophy (22), it was found that the TCI harm avoidance dimension was significantly higher, lower scores on persistence, self-directedness, and cooperation dimensions, and it was stated that there was no significant relationship between the number of CTG repetitions and TCI scores. In a study investigating Temperament and Character Personality Dimensions in Patients with Non-Specific Musculoskeletal Disorders (23), it was reported that pain patients exhibited a personality profile with high harm avoidance and low self-directedness compared to the control group. It has been stated that patients with non-specific musculoskeletal pain disorders can be described as cautious, insecure and pessimistic, and these patients can be described as having difficulty in taking responsibility, lack of long-term goals, chronically low self-esteem and struggling with identity. It has also been shown that there is a strong correlation between personality dimensions and psychological distress and pain. Compared to controls, fibromyalgia patients had higher harm avoidance and persistence in the temperament dimension, lower self-directedness and higher self-transcendence levels in the character dimensions (24). In a study conducted with patients with ankylosing spondylitis, increased reward dependence and decreased self-directedness scores were detected despite self-transcendence (25). Kuloğlu et al. (25) reported that patients with multiple sclerosis had higher levels of harm avoidance and lower levels of self-directedness and persistence compared to the healthy control group.

Although there are studies in the literature with various personality scales in individuals with scoliosis (16, 17, 19), we did not come across any study using the Temperament and Character Inventory (TCI), which is frequently used in determining personality development levels. In this study, it was aimed to determine what the temperament and character traits in young men diagnosed with idiopathic scoliosis are and whether these personality traits differ between healthy and patient groups.

MATERIAL AND METHOD

The study was carried out with the permission of Clinical Research Ethics Committee of Istanbul Haydarpaşa Numune Training and Research Hospital (Date: 12.06.2017, Decision No: 2017/470). The patients included in the study were informed about the study and their written consent was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Military service is compulsory in Turkey and all men are referred to military health examinations by military service branches during the recruitment process. The health condition that is not suitable for military enlistment is decided by the health board in accordance with the military medicine directive and rejected.

The health board consists of specialist physicians in internal medicine, surgery, orthopedics, otolaryngology, ophthalmology, psychiatry, neurology and other specialties when necessary. Routine biochemical examinations of military candidates are performed at the examination of the health board, and chest X-ray and lumbosacral anteroposterior radiographs are taken.

This study was conducted by the orthopedics and traumatology department of our institution and the department of psychiatry between July 2017 and June 2018. The study group consisted of 162 male patients who applied to the orthopedics and traumatology department for a military health board examination on the specified dates, were diagnosed with idiopathic scoliosis in both clinical and radiological radiographs taken with the Cobb method, and accepted to participate in the study. Cases without a disease that could cause idiopathic scoliosis were included in the study. The participants did not have any complaints of idiopathic scoliosis or significant deformity.

The control group consisted of 162 healthy individuals who applied to the Orthopedics and Traumatology Department for examination by the military health board on the same days, were not diagnosed with idiopathic scoliosis in the examinations, had the same age and socio-demographic characteristics as the study group, and agreed to participate in the study. These individuals were evaluated by a psychiatrist according to DSM V diagnostic criteria. It was learned that he did not have any psychiatric disorders before.

Inclusion criteria were 18 years of age and older, adequate level of education (at least primary school graduates) and capable of taking the tests and structured interview form, agreed to participate in the study, diagnosed with IS and did not have any psychiatric follow-up and treatment history. Individuals who were younger than 18 years of age, did not accept to participate in the study, had psychiatric disorders according to DSM V diagnostic criteria, additional medical disorders, and who were not at the level of education to take the tests and structured interview form were excluded from the study.

Those with idiopathic scoliosis (n=162) were confirmed with thoraco-lumbar standing radiographs as a result of orthopedic and radiological examination. Normal spinal curvature was considered a Cobb angle of less than 10 degrees. Individuals who were younger than 18 years of age, did not agree to participate in the study, had psychiatric disorders according to DSM V diagnostic criteria, had additional medical diseases, and were not at the level of education to read and understand the tests and the structured interview form were excluded from the study.

Data Collection Tools

Socio-demographic data form: This form developed by the researchers to determine the socio-demographic characteristics of the participants (age, education level, marital and occupational status, suicide attempt, substance use, smoking and alcohol use etc.) in accordance with the purpose of the study.

Measurement of Cobb angle: The Cobb angle is determined according to the Cobb method by measuring the angle between two horizontal lines are drawn on an X-ray parallel to the upper end-plate of the superior vertebra and the inferior end-plate of the inferior vertebra of the curve (26).

Temperament and character inventory (TCI): It is a self-assessment scale consists of 240 items developed based on Cloninger's theory of personality (21). TCI includes questions that assess four temperament dimensions (novelty seeking, harm avoidance, reward dependence, and persistence, and three-character dimensions (self-directedness, cooperativeness, and self-transcendence). In the temperament dimension, NS has four subscales (NS1: exploratory, NS2: impulsiveness, NS3: extravagance, NS4: disorderliness), HA has four subscales (HA1: anticipatory worry, HA2: fear of uncertainty, HA3: shyness, HA4: fatigability), RD has three subscales (RD1: sentimentality, RD2: attachment, RD3: dependence). In the character dimension, SD has five subscales (SD1: responsibility, SD2: purposefulness, SD3: resourcefulness, SD4: self-acceptance, SD5: congruence), CO has five subscales (CO1: social acceptance, CO2: empathy, CO3: helpfulness, CO4: compassion, CO5: integrated conscience), ST has three subscales (ST1: self-forgetfulness, ST2: trans-identification, ST3: spiritual acceptance). Scales consist of the sum of all subgroups (20, 21). Turkish validity and reliability study of TCI in our country was carried out by Köse et al. (27).

Statistical Analysis

Statistical analysis was performed using the SPSS (ver.22.0, Chicago, II, USA) program. Frequency, percentage, mean value and standard deviation were used to define the data. Whether the data were suitable for normal distribution was examined with the Kolmogorov Smirnov test, with the help of which it was decided to examine the scale scores with parametric tests. Chi-square test was used to compare categorical variables, and one-way analysis of variance (ANOVA) was used to compare numerical values. Independent sample t-test was used to compare the subscale scores of the patient and control groups. In statistical interpretations, $p<0.05$ values were considered significant at the 95% confidence interval.

RESULTS

The mean age of the individuals participating in the study was 22.86±1.73 in young men diagnosed with idiopathic scoliosis and 22.77±1.62 in the healthy control group. The minimum age was 19 and the maximum age was 27. The table containing the findings regarding the variables of age, education level, marital status and income level of the participants are given below (**Table 1**).

Table 1. Sociodemographic information of the participants

Variables	Scoliosis		Control	
	Frequency (n)	Percent (%)	Frequency (n)	Percent (%)
Marital status				
Married	4	2.5	4	2.5
Single	158	97.5	158	97.5
Education status				
Primary education	27	16.7	26	16.0
High school	63	38.9	44	27.2
University	69	42.6	91	56.2
Other	3	1.9	1	.6
Income				
Low	48	29.6	37	22.8
Middle	109	67.3	124	76.5
High	5	3.1	1	.6
Age (Me./S.D.)	22.86±1.73		22.77±1.62	

Me: Mean, S.D.:Standard deviation.

When **Table 1** is examined; 42.6% of those with IS were university graduates, 97.5% were single, and 67.3% had a middle-income level. It was determined that 56.2% of the individuals in the control group were university graduates, 97.5% were single, and 76.5% had a middle-income level. There was no statistically significant difference between the participants in terms of age, education level, marital and income status (p>.05).

There was no significant difference between the groups according to the total/subscale scores of novelty seeking, harm avoidance and reward dependence in temperament dimensions. (p>.05). However, the persistence score of individuals with IS was significantly lower than the healthy control group (p<.05). Compared to control group, there was a statistically significant difference only in the novelty seeking/disorderliness subscale (p<.05) for study group, while there was no statistically significant difference in the other subscale scores (p>.05, **Tables 2** and **3**).

There was no significant difference between the groups in the total/subscale scores of the character dimensions (p>.05, **Tables 2** and **3**).

Table 2. Comparison of the total scores given to the subscales of the Temperament and Character Inventory (TCI) scale by scoliosis group and healthy individuals.

	Scoliosis Me.±.S.D.	Control Me.±.S.D.	Statistical Analysis		
			t	df	p
Novelty seeking	15.03±3.66	15.56±3.85	1.273	322	.204
Harm avoidance	11.49±5.19	10.80±5.30	1.176	322	.241
Reward dependence	13.87±2.80	14.09±2.77	.698	322	.486
Persistence	5.89±1.37	6.20±1.38	2.019	322	.044*
Self-direction	31.27±5.59	31.54±5.85	.427	322	.670
Cooperativeness	32.40±4.27	32.15±5.61	.435	300.6	.664
Self-transcendence	19.44±5.21	19.07±5.03	.662	322	.509

*p<0.05, Me.:Mean, S.D.: Standard deviation, t: Independent sample t-test.

Table 3. Comparison of the scores of the sub-dimensions of the Temprament and Character Inventory (TCI) scales

	Scoliosis Me.±.S.D.	Control Me.±.S.D.	Statistical Analysis		
			t	df	p
Novelty seeking (NS)					
NS1	6.07±1.42	6.15±1.42	-.510	322	.611
NS2	2.98±1.43	2.81±1.78	.963	307.5	.336
NS3	3.37±1.67	3.60±1.61	-1.296	322	.196
NS4	2.61±1.55	3.00±1.79	-2.095	322	**.037***
Harm avoidance (HA)					
HA1	3.75±1.97	3.82±2.09	-.300	322	.764
HA2	3.02±1.51	2.82±1.63	1.166	322	.244
HA3	1.99±1.56	1.85±1.69	.811	322	.418
HA4	2.72±1.94	2.31±1.93	1.869	322	.063
Reward dependence (RD)					
RD1	6.50±1.96	6.25±1.83	1.102	322	.230
RD2	4.94±1.79	5.20±1.52	-1.371	313.7	.171
RD3	2.43±1.42	2.64±1.33	-1.414	322	.158
Persistence (P)	5.89±1.37	6.20±1.38	-2.019	322	**.044***
Self-direction (SD)					
SD1	5.81±1.64	5.85±1.79	-.195	322	.369
SD2	5.86±1.22	5.81±1.22	.364	322	.918
SD3	3.80±1.13	3.81±1.13	-.098	322	.520
SD4	6.46±2.47	6.43±2.28	.094	322	.292
SD5	9.33±1.72	9.62±1.63	-1.594	322	.383
Cooperativeness (C)					
C1	6.77±1.08	6.67±1.31	.740	322	.460
C2	5.06±1.21	5.04±1.46	.124	322	.901
C3	4.97±1.19	5.07±1.52	-.692	304.8	.489
C4	8.59±1.71	8.27±2.02	1.575	322	.116
C5	7.00±1.28	7.10±1.50	-.638	322	.524
Self-transdence (ST)					
ST1	6.06±1.87	5.87±1.95	.903	322	.367
ST2	6.28±1.80	6.36±1.87	.648	322	.717
ST3	7.10±2.79	6.84±2.64	.630	322	.391

*p<0.05, Me.:Mean, S.D.: Standard deviation, t: Independent sample t-test. NS1: exploratory, NS2: impulsiveness, NS3: extravagance, NS4: disorderliness, HA1: anticipatory worry, HA2: fear of uncertainty, HA3: shyness, HA4: fatigability, RD1: sentimentality, RD2: attachment, RD3: dependence, SD1: responsibility, SD2: purposefulness, SD3: resourcefulness, SD4: self-acceptance, SD5: congruence, C1: social acceptance, C2: empathy, C3: helpfulness, C4: compassion, C5: integrated conscience, ST1: self-forgetfulness, ST2: trans-identification, ST3: spiritual acceptance.

DISCUSSION

In this study, we evaluated personality traits in young men diagnosed with idiopathic scoliosis using TCI and compared them with the normal population. The main

finding of this study is that the persistence temperament dimension scores of study group are lower than those of healthy individuals. In addition, we found lower scores in the disorderliness, which is one of the subscales of novelty seeking. There was no significant difference in the other sub-dimensions of TCI compared to the control group. This situation can be explained by the fact that due to the TCI consists of 240 questions, takes about 30 minutes, and the participants will go to other clinics for the health board examination, they have to fill out the questionnaire randomly. In addition, the mean scores of the other sub-dimensions of TCI were not different from the normal group, since the participants did not have any symptoms suggestive of idiopathic scoliosis and the diagnosis of scoliosis was made by incidentally. To our knowledge, our study is the first to evaluate temperament and character traits with TCI in patients with IS.

Idiopathic scoliosis is more common in women (3-5). Interestingly, the participants in our study were young adults. The fact that the study was performed on young men may be associated with the homogeneity of the sample group. Young adulthood is a period in which the individuals enter the last steps of identity formation and seeks the identity that identifies with themselves. According to Arnett (29), although identity-related constructions begin in adolescence, basic research and experiences occur in adulthood. In addition to psychosocial, physical, affective, cognitive, and psychomotor development tasks, individuals in the young adulthood period are faced with fulfilling some developmental tasks such as identity crisis, adapting to social values and reaching social maturity (30). In our study, we found that there are differences in temperament and character traits in individuals with IS in this age group compared to control group.

In the literature, personality traits were evaluated with various personality tests in individuals with IS such as Maudsley Personality Inventory (16), Erich Mittenecker and Walter Toman Personality test (19), and Korean Military Multiphasic Personal Inventory (17). In our study, evaluation of personality traits in patients with idiopathic scoliosis was performed with TCI for the first time in literature. Thus, the personality traits of patients with IS were discussed from a different perspective.

Personality traits including temperament and character dimensions have been investigated in studies conducted in medical conditions involving the spine, such as classical myotonic dystrophy non-specific musculoskeletal disorders, fibromyalgia, multiple sclerosis, and ankylosing spondylitis (22-25, 28).

In a study conducted in patients with Classical Myotonic Dystrophy (22), it was reported that TCI was significantly higher in harm avoidance, lower scores in persistence, self-direction and cooperation, and there was no significant relationship between the number of CTG repetitions and TCI scores. In another study conducted in Patients with Non-Specific Musculoskeletal Disorders (23), it was reported that pain patients exhibited higher harm avoidance and lower self-directedness personality profile compared to the control group. It has been stated that patients with non-specific musculoskeletal pain disorders can be described as cautious, insecure and pessimistic, and these patients can be described as having difficulty in taking responsibility, lack of long-term goals, chronically low self-esteem and struggling with identity. It has also been shown that there is a strong correlation between personality dimensions and psychological distress and pain.

In a study performed in fibromyalgia patients, it was reported that harm avoidance and persistence levels were higher than the healthy control group. In this study, it has been suggested that fibromyalgia patients have a tendency to change their level of rigor in coping with life difficulties and continue their activities even if they are exhausted, and that high levels of persistence may adversely affect the coping strategies of fibromyalgia syndrome patients (24). In a study conducted in ankylosing spondylitis patients (25), a negative correlation was found between self-directedness and Bath ankylosing spondylitis activity index, and between reward dependence and visual analog scale scores. This showed that temperament and character dimensions in patients with ankylosing spondylitis were associated with disease activation and that the disease course was more severe in patients with low scores in these TCI dimensions. In a study with multiple sclerosis patients, it was reported that the patient group had higher levels of harm avoidance and lower levels of self-directedness and persistence compared to the healthy control group (28). It was stated that there were differences between the multiple sclerosis patients and the control group in terms of temperament and character traits. In our study, it was determined that the level of persistence decreased in individuals with IS compared to healthy controls.

Another clinical feature of IS is the patients' dissatisfaction with their body appearance (18). Body appearances can cause individuals to have difficulties in expressing themselves, in their relationships with their peers and parents, and may cause differences in their personality traits (31). In studies conducted in obese individuals, in which dissatisfaction with their body appearance was clearly felt, differences were found in temperament and character traits compared to the control group (32, 33). In some studies, it has been reported that obese individuals have higher levels of harm avoidance and

persistence (32). In another study, it was stated that while novelty seeking levels increased, there was a decrease in persistence and self-management levels (33).

Individuals with a high level of persistence show continuity in their behaviors against fatigue and shyness. On the other hand, people with low persistence are inactive, lazy, easily giving up, modest, unsuccessful and defeatist (33). The findings of our study confirm that individuals with IS are with low persistence scores, even if they are asymptomatic, they built up a sedentary life by adapting to their current medical conditions compared to the control group. Moreover, a low persistence score may be associated with the asymptomatic or progressive course of idiopathic scoliosis, as well as with decreased resilience of patients in response to difficulties due to physical and emotional destruction. From this point of view, low level of persistence can be considered as a determining feature in terms of the psychosocial status of patients with IS during diagnosis and treatment.

As can be seen, there are differences between temperament and character traits in studies on some diseases related to the musculoskeletal system. These differences may be related to the sample group of the study, the number of samples, the severity of the disease, whether it is treated or not, whether they cause appearance and deformity, and whether they affect the quality of life. While the findings of our study show parallelism with the findings of some studies (22,28,33), they differ with the findings of some studies (23,25,32).

Another finding of our study is that there is a decrease in the level of regularity-disorderness (NS4), one of the subscales of novelty seeking, in scoliosis patients compared to healthy controls. In a study by Mancuso et al. (34), it was reported that those with body dysmorphic disorder (BDD) had lower novelty seeking scores than those without. These data suggest that BDD patients can be described as slow-tempered, unquestioning, patient, thoughtful, frugal, tolerant of monotony, and tending to be orderly (20,21).

Those who score high on the NS4 subscale tend to be irritable and disorganized, and often vent their anger when they don't get what they want and when they want it. They often prefer activities without strict rules and regulations. They are not prescriptive. They avoid situations that are physically or psychologically frustrating, boring, or uncomfortable for them. In contrast, individuals scoring low on this subscale tend to be organized, orderly, methodical, and systematic, and often prefer activities with strict rules and regulations. They may delay gratification when disappointed for longer than most people. They react slowly in projecting their anger outward (21). In our study, individuals with IS had a lower level of NS4 subscale compared to the control group, indicating that these individuals tended more towards activities that do not force them too much and have clear rules. This may be evidence of the limited social activities of individuals with scoliosis, their use of systematic methods to improve themselves, and the psychosocial problems they experience.

There are some limitations in our study. First, the study participants consisted of young adult males. Therefore, we could not compare temperament and character traits in young adults according to gender. Second, the findings may not allow for generalization because the participants were all male and the study design was cross-sectional. Finally, the TCI is a self-report test and may be affected by environmental conditions. Some items of this scale may be difficult for patients to read and understand, and the support of the researcher may be needed.

CONCLUSION

As a result, it is seen that young men diagnosed with idiopathic scoliosis have low levels of persistence and novelty seeking/disorderness subscale. Idiopathic scoliosis is a disease that affects individuals' body image, motivation levels, self-confidence, quality of life and personality development. It is important for the prognosis of the disease that clinicians dealing with these individuals consider their personality traits during the diagnosis and treatment process. Since the deformity levels of scoliosis affect personality traits, studies evaluating the personality traits of scoliosis patients with different deformity levels are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Research Ethics Committee of Istanbul Haydarpaşa Numune Training and Research Hospital (Date: 12.06.2017, Decision No: 2017/470).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Weinstein SL, Dolan LA, Spratt KF, Peterson KK, Spoonamore MJ, Ponseti IV. Health and function of patients with untreated idiopathic scoliosis: A 50-year natural history study. JAMA 2003; 289: 559-67.
2. Fadzan M & Bettany-Saltikov J. Etiological theories of adolescent idiopathic scoliosis: Past and present. Open Orthop J 2013; 29: 1466-89.
3. Konieczny MR, Şenyurt H, Krauspe R. Epidemiology of adolescent idiopathic scoliosis. J Child Orthop 2013; 7: 3-9.
4. Hresko MT, Talwalkar V, Schwend R. Early detection of idiopathic scoliosis in adolescents. J Bone Joint Surg Am 2016; 98: e67.
5. Yılmaz H, Zateri C, Özkan AK, Kayalar G, Berk H. Prevalence of adolescent idiopathic scoliosis in Turkey: An epidemiological study. Spine J 2020; 20: 947-55.
6. Grauers A, Einarsdottir E, Gerdhem P. Genetics and pathogenesis of idiopathic scoliosis. Scoliosis 2016; 11: 45.
7. Weinstein SL. The natural history of adolescent idiopathic scoliosis. J Pediatr Orthop 2019; 39: 44-6.
8. Aebi M. The adult scoliosis. Eur Spine J 2005; 14: 925-48.
9. Smith FM, Latchford G, Hall RM, Millner PA, Dickson RA. Indications of disordered eating behaviour in adolescent patients with idiopathic scoliosis. J Bone Joint Surg Br 2002; 84: 392.
10. Pyatakova GV, Okoneshnikova OV, Kozhevnikova AO, Vissarionov SV. Psychological aspects of treatment and rehabilitation of patients with adolescent idiopathic scoliosis: Research analysis. Pediatr Traumatol Orthop Reconstr Surg 2019; 7: 103-15.
11. Lehnert-Schroth HRWC, Moramarco MMK. Schroth therapy: advancements in conservative scoliosis treatment. LAP Lambert Academic Publishing; 2018.
12. Fisher S, Cleveland SE. Body image and personality. Princeton, NJ: Nostrand; 1958.
13. Schatzinger LH, Brower EM, Nash Jr CL. Spinal fusion: Emotional stress and adjustment. Am J Nurs Sci 1979; 79: 1608-14.
14. Saccomani L, Vercellino F, Rizzo P. Adolescents with scoliosis: psychological and psychopathological aspects. Minerva Pediatr 1998; 50: 9-14.
15. Freidel K. Psychosocial problems in idiopathic scoliosis. Retrieved from: Berlin: dissertion de; 1999.
16. Kasai Y, Takegami K, Uchida A. A study of patients with spinal disease using Maudsley Personality Inventory. Int Orthop 2004; 28: 56-9.
17. Oh CH, Shim YS, Yoon SH, Park HC, Park CO, Lee MS. The psychopathological influence of adolescent idiopathic scoliosis in Korean male: an analysis of multiphasic personal inventory test results. J Korean Neurosurg Soc 2013; 53: 13.
18. Allen MS, Walter EE. Personality and body image: A systematic review. Body Image 2016; 19: 79-88.
19. Misterska E, Glowacki M, Harasymczuk J. Personality characteristics of females with adolescent idiopathic scoliosis after brace o surgical treatment compared to healthy controls. Med Sci Monit 2010; 16: CR606-15.
20. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993; 50: 975-90.
21. Cloninger CR. Temperament and personality. Curr Opin Neurobiol 1994; 4: 266-73.
22. Winblad S, Lindberg C, Hansen S. Temperament and character in patients with classical myotonic dystrophy type 1 (DM-1). Neuromuscul. Disord 2005; 15: 287-92.
23. Malmgren-Olsson EB, Bergdahl J. Temperament and character personality dimensions in patients with nonspecific musculoskeletal disorders. Clin J Pain 2006; 22: 625-31.
24. Lundberg G, Anderberg UM, Gerdle B. Personality features in female fibromyalgia syndrome. J Musculoskelet Pain 2009; 17: 117-30.
25. Gökmen F, Altınbaş K, Akbal A, et. al. Evaluation of the temperament and character properties of patients with ankylosing spondylitis. Zeitschrift für Rheumatologie 2014; 73: 843-7.
26. Cobb JR. Outline for the Study of Scoliosis. The American Academy of Orthopaedic Surgery Instructional Course Lectures. Ann Arbor, MI: JW Edwars 1948; 5: 261-75.
27. Köse S, Sayar K, Ak İ, Kalelioğlu, U, Kırpınar I, Reeves RA. Temperament and character inventory (Turkish TCI): validity, reliability and factor structure. Bull Clin Psychopharmacol 2004; 14: 107-31.
28. Kuloğlu M, Sağlam S, Korkmaz S, Gürok MG, Üstün SK, Bulut S. Temperament and character traits and alexithymia in patients with multiple sclerosis. Arch Neuropsychiatry 2013; 50: 34-40.
29. Arnett JJ. Emerging adulthood: A theory of development from the late teens through The twenties. Am Psychol 2000; 55: 469-80.
30. Özgüven İE. University students' problems and ways of coping. Hacettepe University Journal of Faculty of Education 1992; 7: 5-13.
31. Auerbach JD, Lonner BS, Crerand CE, et al. Body image in patients with adolescent idiopathic scoliosis: validation of the Body Image Disturbance Questionnaire-Scoliosis Version. J Bone Joint Surg Am 2014; 96: 61.
32. Grucza RA, Przybeck TR, Cloninger CR. Prevalence and correlates of binge eating disorder in a community sample. Compr Psychiatry 2007; 48: 124-31.
33. Sullivan S, Cloninger CR, Przybeck TR, Klein S. Personality characteristics in obesity and relationship with successful weight loss. Int J Obes 2007; 31: 669-74.
34. Mancuso SG, Knoesen NP, Chamberlain JA, Cloninger CR, Kale DJ. The temperament and character profile of a body dysmorphic disorder outpatient sample. Pers Ment Health 2009; 3: 284-94.

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Comparison of prone position effectiveness with percentage of injured lung area in awake non - intubated COVID-19 patients

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ABSTRACT

Aim: Prone position plays a key role in the treatment of both non-intubated and intubated patients because COVID-19 associated respiratory failure is gas exchange abnormalities based on shunt and dead-space ventilation. In this study, we aimed to compare the effect of prone position applied in awake non-intubated COVID-19 patients with percentage of injured lung area.

Material and Method: 65 patients with awake, non-intubated were included in this prospective, single-center study. Percentage of injured lung area was calculated using chest computer tomography taken during diagnosis of patients. The prone position cycle was applied as 6 hours prone, 4-6 hours supine position.

Results: The mean of percentage of injured lung area was 25.16±13.81. When percentage of injured lung area groups were compared with the 0th, 6th, 24th and 48th hour SpO_2/FIO_2 ratio and respiratory frequency; while the SpO_2/FIO_2 ratio increased in all hours with prone position in the 0-10% and 10-30% groups, a decrease was observed in the SpO_2/FIO_2 ratio over time in the ≥ 30% group.

Conclusions: The prone position is a safe and effective application that causes improvement in SpO_2/FIO_2 ratio and RR in awake non-intubated COVID-19 patients with less damage to the lung. However, it should be kept in mind that as the damage to the lung increases, the expected recovery might not be possible.

Keywords: Acute hypoxemic respiratory failure, COVID-19, prone position, critical care, lung injury

INTRODUCTION

Prone position (PP) has been used as a recruitment strategy in acute respiratory distress syndrome (ARDS) patients on mechanical ventilation support since 1976 (1). Prone position application corrects oxygenation by reducing ventilation/perfusion mismatch, providing a more homogeneous transpulmonary pressure distribution and recruitment of non-aerated dorsal regions of the lung by reducing ventral to dorsal axis and causing an increase in lung volume (2). Acute respiratory failure (ARF) has also had positive effects on oxygenation with PP in awake spontaneously breathing non-intubated patients (3). Considering that COVID-19 associated respiratory failure is gas exchange abnormalities based on shunt and dead-space ventilation, PP plays a key role in the treatment of both awake spontaneous breathing non-intubated patients and intubated patients (4). The application of PP can be affected by many conditions such as patient compliance, selected oxygen therapy method, duration of PP, severity of COVID-19 disease, severity of PP and COVID-19 released pulmonary lesions in early or late period (1,5-7)

In this study, we aimed to compare the effect of PP applied in awake non-intubated COVID-19 patients with percentage of injured lung area (ILA).

MATERIAL AND METHOD

65 COVID-19 patients with awake, non-intubated spontaneous breathing were included in this prospective, single-center study after approval by the Muğla Sıtkı Koçman University Ethics Committee (Decision No: 148 Date: 2021). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration. Inclusion criteria for the study is designed to be above 18 years of age, non-pregnant, SARS-CoV-2 RT-PCR test result is positive or COVID-19 pneumonia compatible

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with computer tomography (CT) lung screening patients with symptoms and clinical findings and CT lung screening those who need oxygen therapy in the last 24 hours. Those under the age of 18 and pregnant women and those who did not need oxygen therapy and those who were indicated for intubation were excluded from the study.

Age, sex, medical treatment, oxygen therapy method [non-invasive ventilation (NIV), high flow oxygen (HfO_2), nasal cannula (NC)], percentage of ILA and department in which the patient was admitted (intensive care unit (ICU) / ward) were registered.

Percentage of ILA was calculated using chest CT taken during diagnosis of patients. Chest CT shots were obtained without contrast agent injection, during deep inspiration, in the supine position. Radiological images were obtained with 256-section Toshiba-TCT-60 AX and 4-Section Siemens Somatom device localized in the emergency room only for COVID-19 patients. The parameters of tube voltage 120 kV, tube current modulation 100-250 mAs, spiral pitch factor 0.98 and collimation width 0.625 were used. The images were transferred to the VIA port system located in our hospital workstation and a 3-D reconstruction was made. The images were evaluated on a high-resolution medical screen.

3 lobes on the right lung and 2 lobes on the left lung were separately examined. Each lobe was accepted by 20% and lobe volume was measured. The areas in the view of the consolidated and ground-glass area were calculated by volumetric voxel and calculated on the computer through the program. Their percentages were calculated over the total volume. The percentage values of all lobes were collected and total loss of lung aeration was found.

For the applied PP, the head of the patient lying face down was brought to the right or left side and supported with a thin pillow. On the side where the head was turned, the arm was extended up and the other arm was extended down. A pillow was placed on the dorsal face of the foot to prevent the tips of the toes from coming into contact with the bed and staying under pressure. The position was applied 2 times a day in the form of 4-6 hours. The position cycle was applied as 6 hours PP, 4-6 hours supine position (SP), 6 hours PP and again 4-6 hours SP. Oxygen therapy with NIV, HFO_2, and NC was continued during PP and SP. SpO_2, respiratory frequency, FIO_2 were recorded before PP. The time when the first prone position was given was considered zero, and subsequent follow-ups were repeated at the 6^{th}, 24^{th}, and 48^{th} hours. SpO_2, respiratory rate (RR) and FIO_2 were re-recorded at the 6^{th}, 24^{th} and 48^{th} hours.

FIO_2 value, which was also set in mechanical ventilation in NIV and HFO_2, was recorded. **Table 1** was used to determine FIO_2 at low flow NC. A FIO_2 value corresponding to the oxygen current was obtained.

Table 1. Estimated inspired oxygen concentration (8)

Device	Reservoir Capacity	Oxygen flow (L/min)	Approximate FIO_2
Nasal Cannula	50ml	1	0.24
		2	0.28
		3	0.32
		4	0.36
		5	0.40
		6	0.44

SpO_2/ FIO_2 ratio was calculated from SpO_2 and FIO_2 values for all times.

The presence of invasive mechanical ventilation and intubation days, number of hospital admissions during treatment and discharge patterns (death/survival) were noted.

Statistical Analysis

Statistical analyses were performed using SPSS software version 23. The variables were investigated using analytical methods (Kolmogorow-Simirnov/Shapiro-Wilk test) to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables (SpO_2/FIO_2 ratio and RR values). The Chi-square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups.

The Kolmogorov-Simirnov/Shapira-Wilks test was applied to examine the normal distribution of ILA percentage, SpO_2/ FIO_2 ratio and RR.

The Wilcoxon test was used to compare the change in SpO_2/ FIO_2 ratio and RR between initial 6, 24, 48 hour. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using Spearman test. A p-value of less than 0.05 was considered to show a statistically significant result.

The possible factors identified with univarite analyses were further entered into the Cox regression analysis, with backward section, to determine independent predictors of survival and risk of intubation; only those with clinical significance were included. The proportional hazards assumption and model fit was assessed by means of residual analysis. A 5% type-I error level was used to infer statistical significance.

RESULTS

The study included 75 patients. 6 patients could not tolerate PP and 4 patients were excluded from the study because they were intubated within the first 24 hours.

Statistical evaluation was performed on 65 patients who met the study protocol. 39 (60 %) of the patients were male and 26 (40 %) were female. The average age was 62.53±15.52, the average duration of hospitalization was 13.98±8.38, and the average percentage of ILA was 25.16±13.81. 7 (10,8 %) patients were provided with non-invasive ventilation (NIV), 34 (52,3 %) with HFO_2, 24 (36,9 %) with NC oxygen support. 11 (16.6%) patients were intubated and received invasive mechanical ventilation support, and 10 (15.4) patients died. Dexamethasone was used in the treatment of 30 (46.9%) patients, methylprednisolone was used in 25 (38,4%) patients and immunoglobulin was used 7 (10,8 %) patients. Percentage of ILA was grouped to be 0-10%, 10-30%, 30% and above. Percentage of ILA groups was combined for descriptive statistics. Percentage of ILA ≥ 30% of those with more advanced age, HFO_2 or NIV use, intubation, length of stay in hospital day and exitus were more observed and evaluated as statistically significant (respectively, p-value; 0,041, <0,001, 0,045, 0,013, 0,023) Looking at initial RR and SpO_2/FIO_2 ratio, lower SpO_2/FIO_2 and higher RR were found in the group with percentage of ILA ≥ 30%, and this was statistically significant (p-value <0.001) (**Table 2**).

Compared with percentage of ILA 6th, 24th and 48th hour SpO_2/FIO_2 ratio and RR; moderately negative between the ILA percentage and the 6th and 24th hour SpO_2/FIO_2 ratio (r: -0.466, -0.635, respectively; p value <0.001); and a moderate positive correlation was found with 6th and 24th hour RR (r:0.668, 0.630, respectively; p value <0.001). A strong correlation was found when the percentage of ILA was compared with the 48th hour SpO_2/FIO_2 ratio and respiratory frequency (r: -0.819, 0.980, respectively; p-value <0.001). Low positive correlation was found when the percentage of ILA was compared with invasive mechanical ventilation (r: 0.378; p-value <0.001).

When percentage of ILA groups were compared with the 0th, 6th, 24th and 48th hour SpO_2/FIO_2 ratio and RR; while the SpO_2/FIO_2 ratio increased in all hours with PP application in the 0-10% and 10-30% groups, a decrease was observed in the SpO_2/FIO_2 ratio over time in the ≥ 30% group. Although RR decreased in all groups and at all hours, it was found to be statistically significant only at the 6th hour (**Table 3**).

Table 2. Baseline characteristic of patients and descriptive statistical analyses for percentage of ILA

	Percentage of ILA		Total (n:65)	P values
	0-30% (n: 37)	>30% (n: 28)		
Gender (n)				
Female	73.1% (19)	26.9% (7)	40% (26)	0.42
Male	46.1% (18)	53.9% (21)	60% (39)	
Age (mean ±SD)	41.56±18.29	67.45±14.96	62.53 ± 15.52	0.041*
O_2 Therapy (n)				
Nasal cannula	87.5 % (21)	12.5 % (3)	% (24)	<0.001*
HFO_2 or NIV	39.1 % (16)	60.9 % (25)	%(41)	
Mechanical Ventilation (n)				
Yes	27.3% (3)	72.7% (8)	16.9% (11)	0.045*
No	62.9% (34)	%37.1 (20)	83.1% (54)	
Exitus (n)				
Yes	18.18% (2)	81.8% (9)	15.4 % (11)	0.013*
No	%64.8 (35)	35.18% (19)	84.6% (54)	
Length of stay in hospital (mean ±SD)	8.5±2.22	16.08±8.92	13.98 ± 8.38	0.023*
SpO_2/FIO_2 ratio (mean ±SD)	248.18±26.19	146.53±13.57	204.89 ±108.73	<0.001*
Respiratory rate (mean ±SD)	20.30±3.12	27.85±2.36	23.64 ±4.84	<0.001*

ILA: injured long area HFO_2 : High flow oxygen, NIV: non invaisve ventilation, * p values <0.05

Table 3. Comparison of percentage of ILA with SpO_2 /FIO_2 and RR

	Percentage of ILA			P values
	0-10% (n: 17)	10-30 % (n:20)	>30% (n:28)	
Initial SpO_2/FIO_2 ratio (mean ±SD)	257.47±25.43	241.90±26.76	146.53±13.57	<0.001*
SpO_2/FIO_2 6 hr (mean ±SD)	259.64±28.33	241.95±28.75	137.92±13.30	0.105
SpO_2/FIO_2 24 hr (mean ±SD)	301.70±30.71	252.05±28.97	137.75±13.81	0.001*
SpO_2/FIO_2 48 hr (mean ±SD)	334.94±29.80	270.80±30.47	137.42±14.99	<0.001*
Initial Respiratory rate (mean ±SD)	18.41±2.85	22.20±3.39	27.85±2.36	<0.001*
Respiratory rate 6 hr (mean ±SD)	17.64±2.5	20.70±3.64	25.07±4.12	0.011*
Respiratory rate 24 hr (mean ±SD)	16.23±1.95	20.50±5.17	27.42±4.77	0.149
Respiratory rate 48 hr (mean ±SD)	15.88±2.36	22.60±8.41	27.21±6.74	0.262

SD: standart deviation, ILA: injured long area, RR, respiratory rate, * p values <0.05

Comparison of percentage of ILA with inflammatory markers was shown in **Table 4**.

When looking at the effect of prone position on SpO_2, FIO_2, RR and SpO_2/FIO_2 regardless of percentage of ILA; while an increase in SpO_2/FIO_2 ratio was detected in most of the patients at the 6th and 24th hours according to the baseline; at 48th hour, most of the patients had a decrease in the SpO_2/FIO_2 ratio, and this decrease was statistically significant (p-values; 0.005). Looking at the prone position and RR relationship; RR decreased in all hours with PP application (**Table 5-6**). There was no complication due to PP.

The use of awake-PP did not reduce the risk of being intubated [hazard ratio (RR) 0.1,007 (95% Confidence Interval (CI) 0.981– 1.035), p-value 0.589] and the 28-day mortality risk was not influenced by the use of awake-PP [RR 0,993 (95% CI 0.977-1,009), p-value 0.409)].

DISCUSSION

Although COVID-19 pneumonia fits the ARDS Berlin Definition, it is a specific disease with distinctive phenotypes. Disruption of lung interstitium and vascular endothelium, ventilation perfusion mismatch that disrupts pulmonary vasoregulation and fosters thrombogenesis are considered in the pathogenesis (9). The most characteristic feature is respiratory mechanics incompatible with the severity of hypoxemia (10). In early stage of infection, relatively good compliance is observed in patients against very poor oxygenation. Chest imaging mainly manifests as multiple small patch lesions and interstitial changes, especially in the lung periphery. As the disease progresses, bilateral lungs show a ground-glass pattern. Marini and Gattinoni (11) defined this patient group as 'type L' characterized by low lung elastance, high compliance and lower lung weight. 'Type H', which is

Table 4. Comparison of percentage of ILA with inflammatory markers

		Percentage of ILA			P values
		0-10% (n: 17)	10-30 % (n:20)	>30% (n:28)	
Lymp (103/μL)	Mean ±Sd Min-Max	0.7±0.34 0.22-1.7	0.73±0.33 0.22-1.7	0.66±0.33 0.22-0.99	0.854
D-Dimer (ng/mL)	Mean ±Sd Min-Max	914 .95±883.87 150- 8816	941.65±1326.17 144-8816	2357.08±2470.61 144-8816	0.001*
Ferritin (ng/mL)	Mean ±Sd Min-Max	335.35±439.41 2.68-3145	391.41±466.75 2.68-3145	758.13±483.29 82.2-2000	0.001*
Fibrinogen (mg/dL)	Mean ±Sd Min-Max	317±123.08 127-679	429.34±190.17 88.6-987	418.89±290.17 118-968	0.739
CRP (mg/L)	Mean ±Sd Min-Max	47.33±58.35 4-257	92.87±67.12 9.6-246	107±80.39 20-327	0.001
LDH (U/L)	Mean ±Sd Min-Max	403.28±182.54 167-906	458.5±288.03 227-1403	490.39±370.28 190-1661	0.721

Lymp; Lymphocyte count, LDH; Lactate dehydrogenase, CRP; C-reactive protein, * P-value<0.005

Table 5. Wilcoxon Signed Ranks Test to to compare mean values between SpO_2 /FIO_2 initial and 6,24,48 hour values

Variables	n	Mean Ranks	Sum of Ranks	z	P values
SpO_2 /FIO_2					
6th hr -Initial				-1.400	0.162
Neg Ranks	23[a]	40.70	936.0		
Poz Ranks	32[b]	18.88	604.0		
Ties	10[c]	-	-		
24th hr - Initial				-1.718	0.086
Neg Ranks	27[a]	30.0	810.0		
Poz Ranks	38[b]	35.13	1335.0		
Ties	0[c]	-	-		
48th hr - Initial				-2.803	0.005*
Neg Ranks	38[a]	23.85	644.0		
Poz Ranks	27[b]	39.50	1501.0		
Ties	0[c]	-	-		

a. SpO_2/FIO_2 6-24-48th hr < Initial SpO_2/FIO_2, b. SpO_2/FIO_2 6-24-48th hr > Initial SpO_2/FIO_2, c. SpO_2/FIO_2 6-24-48th hr=Initial SpO_2/FIO_2

Table 6. Wilcoxon Signed Ranks Test to compare mean values between Respiratory rate initial and 6,24,48 hour values

Variables	n	Mean Ranks	Sum of Ranks	z	P values
Respiratory rate (/dk)					
Initial-6 hr				-5.244	>0.001*
Neg Ranks	44[a]	30.53	1343.5		
Poz Ranks	10[b]	14.15	141.5		
Ties	11[c]	-	-		
Initial-24 hr				-2.565	0.010*
Neg Ranks	42[a]	24.71	1038		
Poz Ranks	12[b]	37.25	447.0		
Ties	11[c]	-	-		
Initial-48 hr				-1.252	0.211
Neg Ranks	37[a]	31.16	1153		
Poz Ranks	25[b]	32	800		
Ties	3[c]	-	-		

a. Respiratory rate 6-24-48th hr < Respiratory rate, b. Respiratory rate 6-24-48th hr > Respiratory rate, c. Respiratory rate 6-24-48th hr=Respiratory rate

clinically compatible with typical ARDS and is generally observed in ICU, that is high elastance, low compliance and higher lung weight often appears with consolidations in CT (11). Pleural effusion is rare. The patients present high respiratory drives, strong inspiratory efforts and highly negative intrathoracic pressures (10). Therefore, when pulmonary consolidation is detected in imaging, the disease has already deteriorated and the lungs have been damaged for quite a long time. In our study, we tried to reveal the severity of injury in the lung by calculating the percentage of ILA from the consolidation and ground-glass pattern areas from CT images.

PP used as recruitment maneuver; in ARDS, the compression of the heart and increased lung weight cause an increase in the compliance of the dorsal lung areas that are prone to atelectasis and thus an improvement in gas exchange. PP, which has been used in ARDS patients with mechanical ventilation support for many years, is now also being used in awake non-intubated ARDS patients (1). The prone position that is frequently used in COVID-19 pneumonia, acts with different mechanisms in Type L and type H. PP positively affects oxygenation by providing redistribution of pulmonary blood flow rather than opening collapsed areas as in type H in Type L. We compared the efficacy of PP administered in awake non-intubated COVID-19 patients with percentage of ILA. While Percentage of ILA improves the oxygenation and RR in patients with less than 30%, it has been observed that it has no positive effect on oxygenation in patients with lung damage 30% and above.

The massive number of cases that occur with the COVID-19 pandemic are admitted to hospital and the rapid evaluation respiratory failure have quickly depleted critical care resources, such as respiratory support equipment especially ventilators, HFO_2, and ICU beds. Therefore recruitment maneuvers such as PP have been started to be applied in out-of-ICUs such as emergency services. Coputo et al applied PP to awake non-intubated COVID-19 patients early in the emergency room and showing a significant improvement in peripheral oxygen saturation (12). On the other hand Coppo et al emphasized that PP can be applied safely in out-of-ICUs, and stated that early PP application is effective in improving oxygenation even in short-term resupination. (13). In addition to all these studies, we tried to determine the severity of lung injury with percentage of ILA. We found that PP applied to patients with low percentage of ILA resulted in improvement in oxygenation and RR, while the same improvement was not seen as the percentage of ILA increased.

Regardless of percentage of ILA, when PP is evaluated, its positive effect on SpO_2/FIO_2 ratio and RR is similar to other studies (5,14,15). Despite finding similar results, Ferando et al emphasized that PP does not reduce the risk of intubation and may even delay intubation (16). It has been shown that PP does not reduce the risk of intubation and 72.7% of the intubated patients have 30% and above percentage of ILA in our study. We think that the lack of positive effect of PP on SpO_2/FIO_2 in this patient group can be explained by patient self-inflicted lung injury (P-SILI). Strong respiratory efforts and high respiratory drives that lead to large negative swings in pleural pressure creating excessive lung stress and strain and increased lung edema due to negative trans alveolar pressure may worsen lung injury and result in P-SILI (17).

Our study has potential limitations. The study was designed as a single center. This situation has limited the number of patients. Arterial blood gas sampling was not performed from the patients. The percentage of ILA of the patients were calculated once during the study period. Percentage of ILAs may be higher considering rapid COVID-19 progression.

CONCLUSION

The prone position is a safe and effective application that causes improvement in SpO_2/FIO_2 ratio and RR in awake non-intubated COVID-19 patients with less damage to the lung. However, it should be kept in mind that as the damage to the lung increases, the expected recovery may not be possible. We think that calculating the percentage of ILA of the patients from CT may be a guide when planning prone position..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Muğla Sıtkı Koçman University Ethics Committee (Date: 2021, Decision No: 148).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care 2020; 24: 28.

2. Taboada M, Bermúdez A, Pérez M, Campaña O. Supine versus Prone Positioning in COVID-19 Pneumonia: Comment. Anesthesiology 2020; 133: 1155-7.
3. Scaravilli V, Grasselli G, Castagna L, et al. Prone positioning improves oxygenation in spontaneously breathing non-intubated patients with hypoxemic acute respiratory failure: a retrospective study, Journal of Critical Care 2015; 30: 1390-4.
4. Diehl JL, Peron N, Chocron R, et al. Respiratory mechanics and gas exchanges in the early course of COVID-19 ARDS: a hypothesis-generating study. Ann Intensive Care 2020; 10: 95.
5. Hallifax RJ, Porter BM, Elder PJ, et al; Oxford Respiratory Group. Successful awake proning is associated with improved clinical outcomes in patients with COVID-19: single-centre high-dependency unit experience. BMJ Open Respir Res 2020; 7: e000678.
6. Karpov A, Mitra AR, Crowe S, Haljan G. Prone position after liberation from prolonged mechanical ventilation in COVID-19 respiratory failure. Crit Care Res Pract 2020; 2020: 1-7.
7. Winearls S, Swingwood EL, Hardaker CL, et al. Early conscious prone positioning in patients with COVID-19 receiving continuous positive airway pressure: a retrospective analysis. BMJ Open Respir Res 2020; 7: e000711.
8. Parke RL, Eastwood GM, McGuinness SP; George Institute for Global Health; Australian and New Zealand Intensive Care Society Clinical Trials Group. Oxygen therapy in non-intubated adult intensive care patients: a point prevalence study. Crit Care Resusc 2013; 15: 287-93.
9. Qu J-m, Cao B, Chen R-c. COVID-19 the Essentials of prevention and treatment, First edition, Netherlands: Elsevier; 2021
10. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not?. Crit Care 2020; 154: 1-3.
11. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. JAMA 2020; 323: 2329-30.
12. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. Acad Emerg Med 2020; 27: 375-8.
13. Coppo A, Bellani G, Winterton D, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Med 2020; 8: 765-74.
14. Singh P, Jain P, Deewan H. Awake prone positioning in COVID-19 patients. Indian J Crit Care Med 2020; 24: 914-8.
15. Hahm CR, Lee YK, Oh DH, et al. Factors associated with worsening oxygenation in patient with non-severe COVID-19 pneumonia. Tuberc Respir Dis (Seoul) 2021; 84: 115-2.
16. Ferrando C, Mellado-Artigas R, Gea A, et al. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Crit Care 2020; 24: 597.
17. Telias I, Katira BH, Brochard L. Is the prone position helpful during spontaneous breathing in patients with COVID-19? JAMA 2020; 323: 2265-7.

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The efficacy of ultrasound and low-intensity laser therapy in carpal tunnel syndrome

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ABSTRACT

Aim: The most frequent type of peripheral entrapment neuropathy is carpal tunnel syndrome (CTS), which is caused by compression of the median nerve at the wrist level. Ultrasound (US) and low-intensity laser therapy (LILT) are among the most commonly used physical therapy methods in the treatment of CTS. The aim of this study is to examine the efficacy of US and LILT in the treatment of CTS and their superiority to each other.

Material and Method: Patients who were admitted to the physical therapy program with the diagnosis of CTS in our clinic were retrospectively examined. A total of eleven patients (18 wrists) diagnosed with mild and moderate CTS were included in our study with the G-Power program with a 5 % margin of error and 80 % power. Patients were divided into US and LILT groups using a simple randomization method. The patients were evaluated in terms of clinical and electrophysiological parameters before and after treatment.

Results: A total of 18 wrists were included in our study, of which eight patients were diagnosed with mild CTS and the rest (n=10) with moderate CTS. The mean age of the patients was 49.66±10.68 years. When the post-treatment clinical (Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), hand and pinch grip strength, measurement of wrist joint range of motion) and electrophysiological parameters were evaluated between the US and LILT groups, no significant difference was found in terms of their superiority over each other ($p>0.05$). When the LILT group was compared before and after treatment, a statistically significant difference was found in the degree of wrist extension, handgrip strength and BCTQ parameters. ($p<0.05$).

Conclusion: When US and LILT were compared in patients with mild and moderate carpal tunnel syndrome, no significant difference was found between the groups in terms of clinical and electrophysiological parameters. However, a statistically significant difference was found in the LILT group in terms of some clinical parameters before and after treatment.

Keywords: Low-intensity laser therapy, ultrasound, carpal tunnel syndrome

INTRODUCTION

Carpal Tunnel Syndrome (CTS) is the most common clinical entrapment mononeuropathy caused by compression of the median nerve at the wrist level (1). Its prevalence is around 3-6% (2). It is more common in females between the ages of 40 and 60 and is usually bilateral (3). Most patients complain of one or more of the symptoms such as weakness, pain, numbness or tingling in the hand, especially in the thumb, index and middle fingers (4). The severity of these symptoms increases at night and may wake the patient from sleep (5). CTS risk factors can be chronic diseases such as diabetes mellitus or functional disorders of the thyroid, as well as pregnancy, high body mass index, repetitive traumas (2). The most frequently used tests in the clinic for diagnosis are Tinel and Phalen tests, but the most reliable objective method is electrodiagnostic tests (6).

Conservative treatments used to manage CTS are diverse. Some of the commonly used are tendon gliding exercises, wrist splinting, local corticosteroid injections, and physical therapy modalities (7,8). The most commonly used physical therapy modalities are low-intensity laser therapy (LILT) and ultrasound (US) therapy (9). It is thought that these two methods have biophysical effects on nerve tissue and facilitate nerve healing by stimulating regeneration (10).

The aim of this study is to examine the efficacy and superiority of LILT and US therapies used in the treatment of patients with CTS, using clinical and electrophysiological parameters.

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MATERIAL AND METHOD

The study was initiated with the approval of the Research Ethics Committee of Amasya University (Date: 08/10/2020, Decision No: 2020/117). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

The study was planned as a retrospective. In the test performed with the G-Power program with 5% margin of error and 80% power, it was revealed that the groups should have at least seven people. The study groups consisted of patients who applied to the Amasya University Physical Therapy and Rehabilitation polyclinic with complaints of pain and tingling in the wrist between November 2020 and January 2021. Clinical examination and electroneuromyography (ENMG) were used to diagnose CTS. Median nerve conduction studies were performed on all patients, and patients were classified as mild, moderate, and advanced according to the American Electrodiagnostic Medical Association guidelines (11). According to this guidelines, (a) Normal means no electrophysiological abnormality (b) Mild CTS represents the reduction in sensory conduction velocity (SCV), distal motor latency (DML) is within normal limits; (c) Moderate CTS: prolongation of DML, slowing of SCV (d) Severe CTS: It means the prolongation of the DML and the absence of sensory conduction. (12-14).

Patients diagnosed with mild or moderate CTS were included in the study. Patients with advanced CTS diagnosis, surgical operation in the wrist region, fractures in the nearby region and metal or implants in the vicinity of the wrist region were not included in the study. Wrist splint was prescribed to all patients. Included patients were randomly divided into two groups, US and LILT, by simple randomization (www.randomizer.org).

After obtaining the demographic data of the patients, the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) was administered to each patient. BCTQ consists of two sub-sections as Symptom Severity Scale (SSS) and Functional Status Scale (FSS). A high score indicates the severity of symptoms and inadequate functional status (15). Turkish validity and reliability were established (16). ENMG evaluations of the patients participating in the study were made by the same physiatrist at room temperature with the Nihon-Kohden MEB-9400K (Nihon Kohden Corp, Tokyo, Japan) EMG device.

A hand dynamometer (Baseline Dynomometer, New York, USA) was used to evaluate the handgrip strength of the patients, and a pinch meter (Baseline Pinchmeter, New York, USA) was used to evaluate the pinch grip strength. While measuring the handgrip, it was measured using level 2 resistance (3.75 cm) with the elbow in 90° flexion and the forearm and wrist in neutral position. Maximum contraction was requested from the patients, adequate rest intervals were given, and the measurements were taken 3 times and the average was recorded as kilograms. Pinch grip strength was evaluated by squeezing the metal part of the pinch meter with the thumb tip on one side and the index fingertip on the other side. The average of 3 repetitions given an adequate rest interval was recorded (17).

Measurements of wrist joint range of motion are one of the measurable parameters that inform us about the functional status of the hand in CTS patients (18). When measuring wrist flexion and extension, the pivot point is taken as the styloid process of the radius and the fixed arm of the goniometer is at the radius. The movable arm followed the second metacarpal bone. While measuring the wrist radial and ulnar deviations, the forearm was kept on the table in the prone position, then the fixed arm of the goniometer was placed on the midline of the forearm and the movable arm was placed on the third metacarpal bone (19).

ROM and grip strength measurements were performed by the same physiotherapist. Evaluations (ENMG, ROM, grip strength) were made for all patients before and after treatment. The patient evaluations before the study started and on the 30th day after the treatment sessions were statistically compared.

Treatment Protocol

All patients received 10 sessions of physical therapy, 5 sessions per week. Patients in the US group were given 1 MHz frequency, 1.0 W/cm² intensity, and 3-minute pulsed type US therapy with a mobile US device (Chattanooga 2776, USA). In the LILT group, 904 Nm wavelength, 9J and 5-point application laser device was applied to the wrist for 5 minutes, with the patient and therapist taking the necessary safety precautions.

Statistical Analysis

Research data was uploaded to the computer environment and evaluated by means of SPSS® version 21.0 statistical package program (SPSS Inc., Chicago, IL, USA). In order to ensure that the selection of the patients to the study groups was random, they were divided into two groups using a simple randomization program. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk Test). Descriptive statistics were presented as mean±standard deviation and median (25%-75%). The Independent Groups T-Test was used for the statistical significance between two independent groups for the variables found to have a normal distribution. Paired T Test was used as a statistical method for statistical significance between two dependent groups. For the variables that do not

show normal distribution; Mann-Whitney U Test was used for significance between two independent groups and Wilcoxon Signed Rank Test was used between two dependent groups.The results were evaluated at the 95% confidence interval, statistically at the p<0.05 level.

RESULTS

When the demographic data of the patients were examined, the mean age of the patients was 49.66±10.68 years. Bilateral CTS was diagnosed in seven of the patients included in the study. Only one of the patients were men. When the patients who received treatment were evaluated, eight patients were diagnosed with mild CTS and the rest (n=10) were diagnosed with moderate CTS. The patients were divided into two groups and US (n=8) was applied to one group and LILT (n=10) to the other group. When **Table 1** and **Table 2** were examined, a significant difference was found only in the degree of wrist radial deviation when the parameters before the treatment and at the 1st month were compared in the group receiving US treatment. On the other hand, a statistically significant difference was found in the degree of extension, handgrip strength, BCTQ in the LILT group (p<0.05). No statistically significant difference was found between the US and LILT groups before the treatment in terms of wrist flexion degrees, wrist radial and ulnar deviation degrees, hand and pinch strength values, ENMG and BCTQ parameters, except for the degree of wrist extension (p>0.05). There was no statistically significant difference between the groups in terms of clinical and electrophysiological parameters in the first month after treatment (p>0.05).

Table 1. Comparison of clinical parameters within and between groups before and after treatment

	LILT (n=10)	US (n=8)	p value
Wrist flexion pre	66.6±7.1	65.7±3.7	0.767[a]
Wrist flexion post	69.3±6.0	67.8±3.2	0.558[a]
p value	0.212[b]	0.340[b]	
Wrist extension pre	59.2±5.4	65.8±4.2	0.012[a]
Wrist extension post	66.6±7.2	68.8±9.2	0.567[a]
p value	0.013[b]	0.463[b]	
Wrist radial deviation pre	22.3±8.0	25.5±2.6	0.302[a]
Wrist radial deviation post	22.4±3.6	22.1±2.7	0.864[a]
p value	0.960[b]	0.011[b]	
Wrist ulnar deviation pre	45.3±5.9	46±4.5	0.788[a]
Wrist ulnar deviation post	46.2±6.7	43.5±2.3	0.300[a]
p value	0.718[b]	0.150[b]	
Handgrip pre	51.6±22.7	30.00 (17.0-51.75)	0.075[c]
Handgrip post	63.2±24.3	41.50 (14.0-58.00)	0.075[c]
p value	0.002[b]	0.779[d]	
Pinch grip pre	12.7±6.0	8.7±5.2	0.165[a]
Pinch grip post	13.3±6.3	8.1±3.2	0.052[a]
p value	0.541[b]	0.590[b]	
FSS pre	21.7±6.2	18.50 (13.25 - 31.25)	0.687[c]
FSS post	14.3±5.0	16.50 (12.50 – 18.00)	0.315[c]
p value	0.00[b]	0.105[d]	
SSS pre	27.4±5.8	27.6±9.8	0.953[a]
SSS post	18.1±5.0	23.6±9.5	0.133[a]
p value	0.003[b]	0.363[b]	

a: Independent t test, b: Paired t test, c: Mann-Whitney U test, d:Wilcoxon, Numerical data showing normal distribution are given as mean±standard deviation. Numerical data that do not show normal distribution are given as median(%25-%75). (LILT: Low-intensity laser therapy, US: Ultrasound therapy, Pre: Before treatment, Post: After treatment 1 month, FSS: Functional status scale, SSS: Symptom severity scale)

Table 2. Comparison of electrophysiological parameters within and between groups before and after treatment

	LILT (n=10)	US (n=8)	p value
Median nerve motor amplitude pre	12.9±4.0	12.9±3.2	1.000[a]
Median nerve motor amplitude post	10.8±3.7	11.5±2.9	0.673[a]
p value	0.123[b]	0.300[b]	
Median nerve distal motor latency pre	4.2±0.7	3.83(3.24 – 4.34)	0.360[c]
Median nerve distal motor latency post	4.1±0.5	3.48(3.24 – 4.22)	0.110[c]v
p value	0.659[b]	0.161[d]	
Median nerve sensory conduction velocity pre	37.00(33.25-44.83)	39.10(34.40-47.43)	0.762[c]
Median nerve sensory conduction velocity post	37.45(33.30-42.10)	42.35(37.50-49.03)	0.203[c]
p value	0.878[d]	0.125[d]	
Median nerve motor conduction velocity pre	54.8±5.5	57.7±3.2	0.207[a]
Median nerve motor conduction velocity post	54.5±6.0	59.9±4.7	0.055[a]
p value	0.792[b]	0.341[b]	

a: Independent t test, b: Paired t test, c:Mann-Whitney U test, d:Wilcoxon, Numerical data showing normal distribution are given as mean±standard deviation. Numerical data that do not show normal distribution are given as median (%25-%75). (LILT: Low-intensity laser therapy, US: Ultrasound therapy, Pre: Before treatment, Post: After treatment 1 month, FSS: Functional status scale, SSS: Symptom severity scale)

DISCUSSION

In this study, the efficacy of US and LILT therapies in patients diagnosed with CTS in the physical therapy outpatient clinic was compared in terms of clinical and electrophysiological aspects. Although there are many studies in the literature comparing the efficacy of US and LILT treatment in CTS (20-22), no study has been found that evaluated the measurement of wrist joint range of motion (extension, flexion, radial and ulnar deviation), BCTQ, hand and pinch grip, and ENMG.

CTS is a disease that is common in society and negatively affects people's daily living activities. Various conservative and surgical treatment methods are used in the treatment of CTS (23). Although surgery is an effective treatment option, non-invasive methods are the first choice in treatment because of the possibility of recurrence, complications, and failure. Conservative treatment methods include; splinting, injections, physical therapy and alternative therapies (24,25). LILT and US are more prominent among physical therapy modalities. Although numerous studies have been conducted in the literature, there is no consensus on the efficacy and superiority of these treatments (25).

US is one of the physical therapy agents commonly used in the treatment of musculoskeletal pain. US converts electrical energy into sound waves. As it passes through the tissues, it acts by creating heat according to the tissue resistances (26). There are numerous research on the use of US in the treatment of CTS in the literature. However, a full judgment has not been reached regarding the effectiveness of US in the treatment of CTS. Ebenbichler et al. (10) evaluated the effectiveness of US therapy in CTS with their study on 45 patients with bilateral CTS, significant improvement in treated wrists was reported at six-month follow-up. Clinical improvement and a substantial electrophysiological change were observed in all groups in another investigation comparing the effectiveness of US treatment at different doses (0 W/cm², 0.8 W/cm², 1.5 W/cm²) in CTS (27). In another study conducted on 30 wrists with mild and moderate CTS, it was found that low-intensity (0.5 W/cm²) US treatment provided clinical improvement but did not show any significant electrophysiological change (28). In a study of 40 patients with a one-year follow-up, Kamalakannan et al. (29) found that US therapy did not produce a clinically significant benefit in CTS. Similarly, in our study it was observed that US treatment did not have a statistically significant effect on clinical and electrophysiological parameters in CTS.

LILT is used to treat chronic painful conditions such as musculoskeletal injuries, arthritic conditions, and postherpetic neuralgia (30,31). The mechanism of action of LILT is thought to be an increase in ATP production, high endorphin levels, and anti-inflammatory effects. It is also known to accelerate collagen synthesis, activate angiogenesis and increase microcirculation (32). The results obtained in previous studies investigating the efficacy of LILT in CTS are contradictory. Shooshtari et al. (33) showed a significant improvement in clinical symptoms, nerve conduction studies, and handgrip strength in the laser group compared to placebo. In another study evaluating the efficacy of LILT in CTS, it was shown that laser therapy was not more effective than placebo on clinical and electrophysiological parameters (34). In our study, while clinical parameters of SSS, FSS, handgrip strength and degree of wrist extension were improved after treatment in patients who underwent LILT, it was observed that LILT had no effect on electrophysiological parameters.

When studies comparing US and LILT are examined, their effectiveness and superiority to each other are still discussed. In a study of 50 patients with CTS, US therapy was found to be more effective than LILT in all clinical and electrophysiological parameters (20). Tikiz et al. (22) suggested that the short-term and medium-term efficacy of US on clinical parameters is greater than that of LILT. However, they did not observe significant differences in electrophysiological parameters. Dincer et al. (21) showed that the combination of US or DYLT with splinting is more effective than splinting alone in the treatment of CTS. However, it has been determined that laser therapy is more effective than US therapy in terms of results such as decreasing symptom severity, relieving pain and increasing patient satisfaction. When the results were examined; however, in our study no superiority was found between US and DYLT in terms of post-treatment clinical and electrophysiological parameters.

The major limitation of our study is that it was planned to study on a small number of patients. It is also considered as not evaluating the long-term effects of US and DYLT. One of the most important limitations is that there is no placebo comparison.

CONCLUSION

US and LILT are non-invasive treatment methods that can be effective in reducing symptoms in the treatment of mild and moderate CTS. However, the advantages of these physical therapy methods over each other have not been fully clarified yet. According to our clinical study, when US and LILT were compared in patients with mild to moderate carpal tunnel syndrome, no significant difference was found between the groups in terms of clinical and electrophysiological parameters after treatment. However, a significant difference was found in the LILT group before and after treatment in terms of

degree of extension, gross grip, FDS and SSS parameters. More research is needed to compare the advantages and efficacies of US and LILT treatments.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of Research Ethics Committee of Amasya University (Date: 08/10/2020, Decision No: 2020/117).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES:

1. Phalen GS. The carpal-tunnel syndrome: seventeen years'experience in diagnosis and treatment of six hundred fifty-four hands. JBJS 1966; 48: 211-28.
2. Kaymak B, Özçakar L. Karpal tünel sendromu. Hacettepe Tıp Derg 2007; 38: 141-6.
3. Serarslan Y, Melek İM, Duman T. Karpal tünel sendromu. Pamukkale Tıp Derg 2008: 45-9.
4. Kamolz L-P, Beck H, Haslik W, et al. Carpal tunnel syndrome: a question of hand and wrist configurations? J Hand Surg 2004; 29: 321-4.
5. Muller M, Tsui D, Schnurr R, Biddulph-Deisroth L, Hard J, MacDermid JC. Effectiveness of hand therapy interventions in primary management of carpal tunnel syndrome: a systematic review. J Hand Ther 2004; 17: 210-28.
6. Evcili G, Gül HL, Karadaş Ö, Börü ÜT. Carpal tunnel syndrome: In which ratio does electroneuromyography confirm the diagnosis? J Clin Analytic Med 2012; 3: 412-4.
7. Piazzini DB, Aprile I, Ferrara PE, et al. A systematic review of conservative treatment of carpal tunnel syndrome. Clin Rehabil 2007; 21: 299-314.
8. O'Connor D, Marshall S, Massy-Westropp N. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Cochrane Database Syst Rev 2003; 2003: CD003219.
9. Rayegani SM, Moradi-Joo M, Raeissadat SA, Bahrami MH, Seyed-Nezhad M, Heidari S. Effectiveness of low-level laser therapy compared to ultrasound in patients with carpal tunnel syndrome: A systematic review and meta-analysis. J Lasers Med Sci 2019; 10: S82.
10. Ebenbichler GR, Resch KL, Nicolakis P, et al. Ultrasound treatment for treating the carpal tunnel syndrome: randomised "sham" controlled trial. BMJ 1998; 316: 731-5.
11. Stevens JC. AAEM minimonograph #26: the electrodiagnosis of carpal tunnel syndrome. American Association of Electrodiagnostic Medicine. Muscle Nerve 1997; 20: 1477-86.
12. Bagga B, Sinha A, Khandelwal N, Modi M, Ahuja CK, Sharma R. Comparison of magnetic resonance imaging and ultrasonography in diagnosing and grading carpal tunnel syndrome: a prospective study. Curr Probl Diagn Radiol 2020; 49: 102-15.
13. Padua L, LoMonaco M, Gregori B, Valente E, Padua R, Tonali P. Neurophysiological classification and sensitivity in 500 carpal tunnel syndrome hands. Acta Neurologica Scandinavica 1997; 96: 211-7.
14. Hirani S. A study to further develop and refine carpal tunnel syndrome (CTS) nerve conduction grading tool. BMC Musculoskeletal Disorders 2019; 20: 1-7.
15. Levine DW, Simmons BP, Koris MJ, et al. A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone Joint Surg Am 1993; 75: 1585-92.
16. Sezgin M, İncel NA, Sevim S, Çamdeviren H, As İ, Erdoğan C. Assessment of symptom severity and functional status in patients with carpal tunnel syndrome: reliability and validity of the Turkish version of the Boston Questionnaire. Disabil Rehabil 2006; 28: 1281-6.
17. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. J Hand Surg 1984; 9: 222-6.
18. Walker J, Sue D, Miles-Elkousy N, Ford G, Trevelyan H. Active mobility of the extremities in older subjects. Physical Ther 1984; 64: 919-23.
19. Cambridge-Keeling. ROM measurement of the hand. Rehabilitation of the Hand and Upper Extremity 5th ed Missouri.169-82.
20. Bakhtiary AH, Rashidy-Pour A. Ultrasound and laser therapy in the treatment of carpal tunnel syndrome. Aust J Physiother 2004; 50: 147-51.
21. Dincer U, Cakar E, Kiralp MZ, Kilac H, Dursun H. The effectiveness of conservative treatments of carpal tunnel syndrome: splinting, ultrasound, and low-level laser therapies. Photomed Laser Surg 2009; 27: 119-25.
22. Tıkız C, Duruöz T, Zeliha Ü, Cerrahoğlu L, Yalçinsoy E. Karpal tünel sendromunda düşük enerjili lazer ve kesikli ultrason tedavi etkinliklerinin karşılaştırılması: plasebo kontrollü bir çalışma. Turk J Phys Med Rehabil Sci 2013; 16.
23. Ekim A, Çolak E. Karpal tünel sendromunda ultrason tedavisi: plasebo kontrollü bir çalışma. Turk J Phys Med Rehabil 2008; 54.
24. Carlson H, Colbert A, Frydl J, Arnall E, Elliot M, Carlson N. Current options for nonsurgical management of carpal tunnel syndrome. Int J Clin Rheumatol 2010; 5: 129.
25. Afşar Sİ, Sarıfakıoğlu B, Yalbuzdağ ŞA. Karpal Tünel sendromu tedavisinde fizik tedavi modalitelerinin yeri: derleme. Turk J Osteoporosis 2014; 20.
26. Klaiman MD, Shrader JA, Danoff JV, Hicks JE, Pesce WJ, Ferland J. Phonophoresis versus ultrasound in the treatment of common musculoskeletal conditions. Med Sci Sports Exerc 1998; 30: 1349-55.
27. Oztas O, Turan B, Bora I, Karakaya MK. Ultrasound therapy effect in carpal tunnel syndrome. Arch Phys Med Rehabil 1998; 79: 1540-4.
28. Piravej K, Boonhong J. Effect of ultrasound thermotherapy in mild to moderate carpal tunnel syndrome. J Med Assoc Thailand=Chotmaihet Thangphaet 2004; 87: S100-6.
29. Jothi KP, Bland JD. Ultrasound therapy adds no benefit to splinting in carpal tunnel syndrome. Muscle Nerve 2019; 60: 538-43.

30. Soriano F, Ríos R. Gallium arsenide laser treatment of chronic low back pain: a prospective, randomized and double blind study. Laser Ther 1998; 10: 175-80.
31. Kemmotsu O, Sato K, Furumido H, et al. Efficacy of low reactive-level laser therapy for pain attenuation of postherpetic neuralgia. Laser Ther 1991; 3: 71-5.
32. Naeser MA, Hahn K-AK, Lieberman BE, Branco KF. Carpal tunnel syndrome pain treated with low-level laser and microamperes transcutaneous electric nerve stimulation: a controlled study. Arch Phys Med Rehabil 2002; 83: 978-88.
33. Shooshtari S, Badiee V, Taghizadeh S, Nematollahi A, Amanollahi A, Grami M. The effects of low level laser in clinical outcome and neurophysiological results of carpal tunnel syndrome. Electromyogr Clin Neurophysiol 2008; 48: 229.
34. Irvine J, Chong SL, Amirjani N, Chan KM. Double-blind randomized controlled trial of low-level laser therapy in carpal tunnel syndrome. Muscle Nerve 2004; 30: 182-7.

Original Article

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Myeloperoxidase deficiency: a single center experience

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ABSTRACT

Aim: Myeloperoxidase (MPO) deficiency is the most common inherited defect of phagocytes. In this article, we aimed to reveal clinical characteristics of our patients with primary MPO deficiency.

Material and Method: In our study, patients aged 0-18 years, who were consulted to Ankara City Hospital Pediatric Hematology Department between 1 October 2019 and 1 December 2021 due to neutropenia, were retrospectively examined. If a patient had neutropenia in the complete blood count and inconsistently normal neutrophil count in the peripheral blood smear formula it was accepted as pseudoneutropenia. Patients with pseuduneutropenia were included in the study.

Results: Fifteen patients diagnosed with MPO deficiency were analyzed in the study. Nine of the patients were female, 6 were male, median age of the patients was 7 (0 – 17.5) years. The mean white blood cell (WBC) count of the patients was reported as 8219±2879/mm³, and the mean neutrophil count and percentage in the complete blood count printout was 33.30±15.88/mm³ and 0,74%±0, 94% respectively. The mean neutrophil count and percentage counted in the peripheral blood smear were 5186±1710 and 63.8%±10.59%, respectively. The mean LUC value on the complete blood count printout was 54.35%±19.47% (Normal range, 0-4%). In the flow cytometry evaluation of peripheral blood samples of the patients, it was observed that neutrophils were stained with CD33, CD13, CD16, CD11b monoclonal antibodies but not with MPO.

Conclusion: Peripheral smear evaluation is important when investigating the etiology of neutropenia. Many hematology analyzers using the MPO staining technique are indicative of MPO deficiency by identifying large unstained cells that do not stain with MPO. In patients who present with recurrent infections and MPO deficiency, other reasons that may predispose to infections should be investigated.

Keywords: Myeloperoxidase deficiency, children, pseudoneutropenia, hematology analyzer, flowcytometry

The study received the 2nd oral presentation award at the 13th National Pediatric Hematology Congress held in Pine Beach Hotel-Antalya between 14-17 October 2021 by the Turkish Pediatric Hematology Association

INTRODUCTION

Myeloperoxidase (MPO) is an iron-containing hemoprotein expressed in azurophilic granules of neutrophils and lysosomes of monocytes. The enzyme has strong antibacterial properties, producing strong bactericidal compounds such as hypochlorous acid from hydrogen peroxide and the halide, chloride (1-3). It is the most common inherited defect of phagocytes. It plays a role in killing various micro-organisms and foreign cells, including bacteria, fungi, viruses, malignant and non-malignant cells (4). Myeloperoxidase deficiency was first described in 1954 and is an autosomal recessive disease caused by mutations in the MPO gene on chromosome 17q23 (5,6). Its incidence was reported as 1:2000-4000 in Europe and America, while it was reported as 1:55000 in Japan (7). Microbial killing is impaired in patients with MPO deficiency, but most patients are asymptomatic, except for the diabetic patients (6). In this article, we aimed to show clinical characteristics of our patients with primary MPO deficiency.

MATERIAL AND METHOD

For all the records examined, the study was carried out with the permission of the Ankara City Hospital Ethics Committee (Date: 22.12.2021, Decision No: E2-21-1178). All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

In our study, patients under the age of 18 years, who were consulted to Ankara City Hospital Pediatric Hematology Department between 1 October 2019 and 1 December 2021 due to neutropenia, were retrospectively examined. If a patient had neutropenia in the complete blood count and inconsistently normal neutrophil count in the peripheral blood smear formula it was accepted as

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pseudoneutropenia. Our study was performed on patients with pseudoneutropenia. To define myeloperoxidase deficiency, a peripheral blood smear prepared using Wright's stain was evaluated and a leukocyte formula was made. The diagnosis of MPO deficiency was primarily considered by confirming a normal population of neutrophils and monocytes in the absence of any atypical or blastic white cells in the peripheral blood smear. To make the definitive diagnosis of the patients, 5 cc blood samples were taken from the peripheral blood to the tube with EDTA and intracytoplasmic MPO staining was performed by flow cytometry. Whether the neutrophils have MPO expression in peripheral blood was evaluated in our hospital by flow cytometry (Beckman Coulter, USA) and using Kaluza software. MPO expressions of cells in the area of neutrophils were examined in the forward scatter / side scatter dot plot. In addition, to differentiate these cells from other cells in peripheral blood, CD45(KO), MPO (PE), CD33 (PC5), CD13 (ECD), CD16 (PB), CD11b (FITC), CD3 (A700), CD19 (A750) by preparing a tube consisting of antibodies, neutrophils and other blood cells were identified, and other surface markers expressed by neutrophils were also examined. In our center, a complete blood count (CBC) is performed from the peripheral blood sample taken into an EDTA tube with the ADVIA 2120i hematology analyzer. The ADVIA 2120i hematology analyzer utilizes a combination of two unique cytochemical methodologies termed collectively as peroxidase activity and nuclear density analysis. In addition, cells larger than normal and unstained on the analyzer output; given as the large unstained cells (LUC) value.

Statistical Analysis

Descriptive statistics were presented as median value (minimum-maximum) for quantitative variables and frequency (percent) for categorical variables. Calculations for descriptive statistics were performed with Statistical Package for Social Sciences (SPSS Version 18.0, Chicago, IL).

RESULTS

Between October 2019 and December 2021, 15 patients were diagnosed with MPO deficiency in the Pediatric Hematology Department of Ankara City Hospital. Nine of the patients were female, 6 were male, median age of the patients was 7 (0–7.5) years. While seven patients were under follow-up due to any chronic disease, neutropenia was detected incidentally in 8 patients at the time of admission to the hospital for any reason. In two patients, neutropenia was detected in the neonatal period. The mean white blood cell (WBC) count of the patients was reported as 8219±2879/mm³, and the mean neutrophil count and percentage in the complete blood count printout was 33.30±15.88/mm³ and 0,74%±0, 94% respectively. The mean neutrophil count and percentage counted in the peripheral blood smear were 5186±1710 and 63.8%±10.59%, respectively. The mean LUC value on the complete blood count printout is 54.35%±19.47% (Normal range, 0-4%). It was observed that the neutrophil counts in the CBCs of all patients were inconsistent with the neutrophil counts counted in the peripheral blood smear. It was determined by peripheral smear examination that none of the patients were neutropenic. In addition, the LUC values of all patients were found to be higher than normal as a result of the hemogram. The laboratory and demographic characteristics of the cases are summarized in **Table**. In the flow cytometry evaluation of the patients' peripheral blood samples, it was observed that neutrophils were stained with CD33, CD13, CD16, CD11b monoclonal antibodies, but not with MPO, and the patients were diagnosed with MPO deficiency.

Table. The laboratory and demographic characteristics of the patients

Patient No	Age (Year)	Gender	Diagnosis of Chronic Disease	Analyzer counts (ADVIA 2120i)				Peripheral blood smear manual count	
				WBC (/mm³)	Neutrophil Count (/mm³)	Neutrophil (%)	LUC (%)	Neutrophil Count (/mm³)	Neutrophil (%)
1	0	K	None	16000	10	0.6	54.4	8800	55
2	6.5	K	ANA +	8830	20	0.2	50.8	4944	56
3	18	K	Granulamatöz Polianjiitis	8180	60	0.7	66.2	7034	86
4	16	K	None	7640	10	0.2	65.4	5195	68
5	11	K	Hypothyroidism	5480	60	1.1	41.8	3836	70
6	1.75	K	Retinoblastoma	4400	20	4	92.4	3432	78
7	7	K	None	10320	30	0.3	71.2	6604	64
8	17	E	None	8050	40	0.5	13	5313	66
9	5	E	Developmental Retardation	5110	50	1	36.3	2350	46
10	3	E	None	9340	30	0.3	56	6351	68
11	15.75	E	Hypertension	8590	40	0.4	63.5	4638	54
12	10	E	None	7560	30	0.4	57.7	5594	74
13	17.5	K	Familial Mediterranean Fever	5030	40	0.8	56.7	2917	58
14	0.16	K	None	7970	40	0.5	24.6	4303	54
15	0	E	None	10790	20	0.2	65.3	6474	60

DISCUSSION

Neutrophils perform their roles in host defense by producing hydrogen peroxide by the oxygen-dependent respiratory burst system, via the myeloperoxidase they contain. Although myeloperoxidase deficiency is one of the most common inherited defects of phagocytosis that can impair microbial killing, it has been rarely reported to be associated with clinical symptoms (4,8). Several point germline mutations cause primary MPO deficiency, such as defective post-translational processing of the myeloperoxidase precursor protein and pre-translational defects caused by mutations in the regulatory part of the MPO gene. Most of the mutations associated with the inherited form are R569W (most common), Y173C, M251T, G501S, and R499C, and deletions of 14 bases (D14) in exon 9 (6). Secondary MPO deficiency is rarer than the inherited form but may develop due to somatic mutations of the MPO gene. In most cases, the deficiency is partial and affects only a portion of the neutrophils, is usually transient, and usually resolves when the underlying condition improves. A variety of disorders, including heavy metal poisoning, severe infections, diabetes mellitus, myelodysplastic syndrome, acute and chronic myeloid leukemia, and Hodgkin lymphoma, are causes of secondary or acquired MPO deficiency (6,9). Secondary MPO deficiency is always accompanied by a disease, and neutrophils have different MPO activity that varies from cell to cell. In the flow cytometric examination of our patients, there was no MPO expression in all neutrophils and monocytes, including those with accompanying chronic diseases. Therefore, we accepted our patients with primary MPO deficiency. While 6 of our patients were under follow-up due to chronic disease, 9 patients did not have an underlying chronic disease and neutropenia was detected at the time of admission to the hospital for any reason. One of our patients had received multiple immunosuppressive therapies for his rheumatological disease, therefore secondary MPO deficiency might have developed. However, we also detected MPO deficiency in the patient's healthy sibling, and the secondary deficiency was excluded. Because, primary MPO deficiency has a genetic origin, occurs with varying degrees of severity in more than one family member, and involves both the neutrophil and monocyte lineages (7,10).

Most patients with MPO deficiency are asymptomatic without an increase in infection, serious infections have been reported in up to 5% of patients (8). Recurrent severe infections with Candida Albicans have been observed in individuals with co-morbidities such as diabetes mellitus (11). It is unclear whether the infections in these patients are solely the result of MPO deficiency or whether other MPO-independent mechanisms are also responsible. Severe infectious complications requiring hospitalization were not observed in any of our patients. Therefore, it is important to diagnose MPO deficiency. It helps us to prevent unnecessary examination and treatment in the follow-up of patients. In the literature in a case series of 4 patients with MPO deficiency, it was reported that one of the patients presented with pneumonia and neutropenia was detected according to the result of the hematology analyzer output, and granulocyte-colony stimulant factor (G-CSF) was administered to the patient. They reported that they subsequently evaluated the patient's peripheral blood smear and found that the patient was not neutropenic (12). One of the main purposes of our article is to emphasize that abnormal results in the hematology analyzer output of the patients should be confirmed by peripheral blood smear. Hematology analyzer ADVIA2120i (Siemens AG), used in our hospital laboratory, separates leukocytes by peroxidase activity and nuclear density. Neutrophil counts are reported to be very low in hemogram results of patients with myeloperoxidase deficiency. The mean neutrophil counts in the laboratory printout of our patients were 33.30±15.88/mm³, while the mean neutrophil counts counted in the peripheral blood smear were 5186±1710/mm³. It gives the LUC value by counting the neutrophils and monocytes that are not stained with myeloperoxidase in the large unstained cell group. Therefore, LUC values in the hemogram printout of patients with MPO deficiency are found to be quite high (12,13). The mean LUC values of our patients were found to be 54.35%±19.47%. These values were seen well above the normal range. Large unstained cells identify blasts, variant, and atypical lymphocytes as well as MPO deficient patients show large neutrophils with reduced MPO activity (14). The increased proportion of large unstained cells should alert the clinician and require peripheral blood smear evaluation to distinguish a pathological condition from normal variants. Myeloperoxidase deficiency can be easily diagnosed in clinical hematology laboratories with flow cytometric examination by evaluating the peroxidase activity of neutrophils from peripheral blood samples (12). We also performed flow cytometric analysis from peripheral blood samples of all our patients. We observed that the neutrophils of the patients were stained with CD33, CD13, CD16, CD11b monoclonal antibodies, but not with MPO. One of our patients was being followed up with a diagnosis of retinoblastoma. However, it is controversial in the literature whether there is a relationship between MPO deficiency and cancer susceptibility (15,16). Our patient number two was being followed up because of anti-nuclear antibody positivity, although he had no clinical findings. Interestingly, in a study, they reported statistically higher MPO plasma levels in SLE patients compared to healthy patients,

but they could not show its relationship with disease severity (17). Our patient number three was diagnosed with granulomatous polyangiitis, and patient number 4 was selected by the pediatric rheumatology department because she was the sister of patient number 3. The patient, who was being followed up with the diagnosis of granulomatous polyangiitis, had received multiple immunosuppressive treatments. It has been reported in the literature that there is a relationship between MPO deficiency and autoimmunity (18). In a study in mice, it was shown that MPO can limit the adaptive immune response by reducing dendritic cell activation, thus reducing both the migration of dendritic cells to the lymph node and the antigen presentation capacity (18). While long-term overproduction of MPO causes tissue damage, it is thought to play an anti-inflammatory role in some cases, depending on the type of inflammation (19).

Because most people with MPO deficiency do not suffer from infections and are typically asymptomatic, prophylactic antibiotics are not recommended. In people with MPO deficiency without comorbidities, specific treatment of infections is sufficient, and no additional treatment is required. The fact that none of our patients had severe infections that required hospitalization also supports this. However, since the incidence of localized and systemic infections is high in patients with diabetes mellitus, rapid and aggressive treatment with antimicrobials is usually required to control infections.

CONCLUSION

Peripheral smear evaluation is important when investigating the etiology of neutropenia. Many hematology analyzers using the MPO staining technique are indicative of MPO deficiency by identifying large unstained cells that do not stain with MPO. In patients who present with recurrent infections and MPO deficiency, other reasons that may predispose to infection should be investigated. Usually, simple laboratory tests and/or clinical presentation and history can distinguish the underlying cause. In patients with MPO deficiency, specific treatment of infections is sufficient, and no additional treatment is required.

The limited number of our patients and the short-term follow-up timeare the limitations of our study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 22.12.2021, Decision No: E2-21-1178).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Xiao X, Saha P, Yeoh BS, et al. Myeloperoxidase deficiency attenuates systemic and dietary iron-induced adverse effects. J Nutr Biochem 2018; 62: 28-34.
2. Domingues-Ferreira M, Levy A, Barros NC, et al. Case report of myeloperoxidase deficiency associated with disseminated paracoccidioidomycosis and peritoneal tuberculosis. Rev Soc Bras Med Trop 2017; 50: 568-70.
3. Albrett AM, Ashby LV, Dickerhof N, et al. Heterogeneity of hypochlorous acid production in individual neutrophil phagosomes revealed by a rhodamine-based probe. J Biol Chem 2018; 293: 15715-24.
4. Yonezawa K, Horie O, Yoshioka A, et al. Association between the neutrophil myeloperoxidase index and subsets of bacterial infections. Int J Lab Hematol 2010; 32: 598-605.
5. Marchetti C, Patriarca P, Solero GP, et al. Genetic characterization of myeloperoxidase deficiency in Italy. Hum Mutat 2004; 23: 496-505.
6. Pahwa R, Modi P, Jialal I. Myeloperoxidase deficiency. 2021 Sep 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29262241. Bookshelf ID: NBK470278,
7. Nauseef WM. Diagnostic assays for myeloperoxidase and myeloperoxidase deficiency. Methods Mol Biol 2014; 1124: 537-46.
8. Lanza F. Clinical manifestation of myeloperoxidase deficiency. J Mol Med 1998; 76: 676-81.
9. Patıroğlu T, Güngör HE, Belohradsky JS, et al. Myeloperoxidase deficiency: the secret under the flag of unstained cell. Turkish J Hematol 2013; 3: 232
10. Larrocha C, De Castro MF, Fontan G, et al. Hereditary myeloperoxidase deficiency: study of 12 cases. Scand J Haematol 1982; 29: 389–97.
11. Cech P, Stalder H, Widmann JJ, et al. Leukocyte myeloperoxidase deficiency and diabetes mellitus associated with *Candida albicans* liver abscess. Am J Med 1979; 66: 149-53.
12. Roh S, Ham JY, Song KE, et al. Myeloperoxidase deficiency manifesting as pseudoneutropenia with low mean peroxidase index and high monocyte count in 4 adult patients. Lab Med 2020; 51: 16-9.
13. Gleghorn DM, Thomas W. Prevalence of myeloperoxidase deficiency determined using an ADVIA 2120i. Int J Lab Hematol 2020; 42: 220-3.
14. Cakir I, Cakir N, Atalay MA, et al. Large unstained cells are correlated with inflammatory biomarkers in patients with invasive aspergillosis. Turkish J Biochem 2018; 43: 306–11.
15. Kutter D, Devaquet P, Vanderstocken G, et al. Consequences of total and subtotal myeloperoxidase deficiency: risk or benefit? Acta Haematol 2000; 104: 10–5.
16. Lanza F, Fietta A, Spisani S, et al. Does a relationship exist between neutrophil myeloperoxidase deficiency and the occurrence of neoplasms? J Clin Lab Immunol 1987; 22: 175-80.

17. Telles RW, Ferreira GA, da Silva NP, et al. Increased plasma myeloperoxidase levels in systemic lupus erythematosus. Rheumatol Int 2010; 30: 779-84.
18. Odobasic D, Kitching AR, Yang Y, et al. Neutrophil myeloperoxidase regulates T-cell-driven tissue inflammation in mice by inhibiting dendritic cell function. Blood 2013; 121: 4195–204.
19. Aratani Y. Myeloperoxidase: Its role for host defense, inflammation, and neutrophil function. Arch Biochem Biophys 2018; 640: 47-52

Original Article

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Distribution of pre- and mid-pandemic transfusions by blood types

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ABSTRACT

Introduction: COVID-19 disease spread rapidly worldwide, causing a pandemic. In this study, we aimed to explore the distribution of blood products in our blood center before and during the pandemic by blood type.

Material and Method: In this study, we retrospectively analyzed 4,271 blood products (1,290 patients) transfused before and during the pandemic through the medical records of Kastamonu Training and Research Hospital Blood Transfusion Center. Moreover, we investigated the associations between transfusions and age, sex, blood type, and COVID-19 infection.

Results: The findings revealed that the majority of the patients receiving transfusions both before and during the pandemic were A Rh (+) (41.4%). Besides, the rates of those with O Rh (+) were 28.8% and 28.7% during the pandemic. In addition, 37 products (28 erythrocyte suspensions, 7 fresh frozen plasma, 2 pooled platelet suspensions) were transfused on 17 patients with confirmed COVID-19.

Conclusion: Transfusions have an important place in the treatment of critically ill patients. The blood type A Rh (+) was previously shown to be associated with an increased risk of COVID-19 infection. In this study, although we realized that products of blood type A were mostly used in general transfusions, transfusions in the pandemic were performed predominantly with blood products of infected patients with blood type O. The modern world is more likely to encounter further pandemics in the future. We think that each region should evaluate its own centers.

Keywords: Transfusion, COVID-19, ABO blood types, rh, blood transfusion center

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INTRODUCTION

COVID-19, emerging in the Wuhan region of China in December 2019, has spread across the world and rapidly turned into a pandemic (1). It is transmitted through the respiratory tract and can be asymptomatic or symptomatic. While the incubation period of the virus is five days on average, 97.5% of symptoms may develop within 11.5 days (2). The research interest in the diagnosis, treatment, predisposing factors, and course of the disease is still fresh. In addition to many domains of life, the disease has affected the regular operations of many hospitals.

Blood transfusion became a relatively safe and viable procedure following the discovery of blood types in the 1900s and early World War I that citrate was a safe and effective anticoagulant (3). As expected, the works of blood centers have also been adversely affected by the pandemic and its undesirable consequences. The pandemic has led to a decrease in blood donations; thus, blood transfusion centers are likely to have difficulty obtaining blood (4,5). Nevertheless, healthcare service delivery should be maintained at its own pace to be able to satisfy the healthcare needs of individuals. Blood transfusion is life-saving and requires a sensitive approach to necessary procedures. For this reason, the proper analysis of blood products is of great importance. In their study, Hof L. et al. recommend taking patient-based measures (preventing anemia, reducing blood loss, etc.) for blood management of intensive care patients, especially due to the decrease in global blood donations owing to the pandemic (6). Ultimately, we aimed to evaluate how our blood center was affected by the pandemic regarding blood products by blood types.

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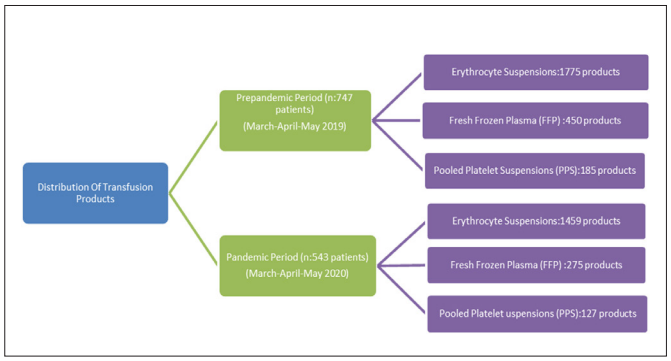
MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Clinical Research Ethics Committee (Date: 14.12.2020, Decision No: 2020-KAEK-143-11). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, we recruited the records of our hospital's blood transfusion center to a retrospective analysis. We compared blood types in all transfusions in 3 busy months of the pandemic in our hospital and those in the same 3 months one year before the pandemic. In total, there were 1,290 patients undergoing blood transfusion, 747 before the pandemic and 543 in the first 3 months in the heyday of the pandemic. Transfusion procedures consisted of 3,234 erythrocyte suspensions (ES), 725 fresh frozen plasma (FFP), and 312 pooled platelet suspensions (PPS). Flow Chart 1 presents the distribution of transfusions by periods, patients, and products.



Flow Chart 1: The distribution of transfusions by periods, patients, and products

We also investigated the patients by age, sex, blood type, COVID-19 infection. Each patient receiving a blood transfusion in the pandemic was recruited to a Real-time polymerase chain reaction (rt-PCR). A definitive diagnosis of COVID-19 positivity was confirmed by our hospital's laboratory. Although some patients tested negative for COVID-19, they were considered suspicious considering their lung tomography imaging findings and received transfusions. Such transfusions were accepted as transfusions to COVID-19-suspected patients.

Statistical Analysis

We encoded and analyzed the data using SPSS version 22 (IBM). While descriptives were shown as numbers and percentages, we performed the Chi-Square test, Kruskal-Wallis test, and Fisher's Exact test to reveal the relationships between the variables. We considered a p-value <0.05 to be significant in all statistical analyses.

RESULTS

The results revealed that the transfusions in both periods significantly differed by sex ($p<0.05$), but it was not the case by age and blood type ($p>0.05$). More than half of the patients (56.4% in the pre-pandemic period and 61.9% in the pandemic period) were over 70 years old, and the distributions were similar for the other age groups. While the percentage of female patients receiving transfusions decreased from 60.8% (pre-pandemic) to 54.9% during the pandemic, the rate of male patients increased from 39.2% to 45.1%. We found that 41.1% of the patients were A Rh (+) in both periods, followed by 0 Rh (+) with the rates of 28.8% and 28.7%, respectively (**Table 1**).

Table 1. Distribution of patients by age, sex, and blood type

Factor	Group	Period		p
		Pre-pandemic	Mid-pandemic	
Age				0.17
	18-30 years	39 (5.2%)	18 (3.3%)	
	31-50 years	78 (10.4%)	55 (10.1%)	
	51-70 years	209 (28.0%)	134 (24.7%)	
	>70 years	421 (56.4%)	336 (61.9%)	
Sex				0.034
	Female	454 (60.8%)	298 (54.9%)	
	Male	293 (39.2%)	245 (45.1%)	
Blood Type				0.087
	A (Rh+)	309 (41.4%)	225 (41.4%)	
	A (Rh-)	47 (6.3%)	28 (5.2%)	
	B (Rh+)	83 (11.1%)	75 (13.8%)	
	B (Rh-)	7 (0.9%)	12 (2.2%)	
	0 (Rh+)	215 (28.8%)	156 (28.7%)	
	0 (Rh-)	37 (5.0%)	14 (2.6%)	
	AB (Rh+)	45 (6.0%)	27 (5.0%)	
	AB (Rh-)	4 (0.5%)	6 (1.1%)	

Considering the blood products (ES, FFP, and PPS), both groups (pre-pandemic and mid-pandemic) did not significantly differ by age and sex ($p> 0.05$). (**Table 2**).

On the product basis, for example, 285 of 309 A Rh (+) patients received ES transfusions in our hospital before the pandemic, and the utilization rate was 92.5%. These 285 patients received a total of 288 × 2.59 (± 2.18)=738 units of ES transfusions (Table 3). On the other hand, the blood types of the patients receiving ES, FFP, and PPS did not significantly differ by transfusion period ($p>0.05$). While more than 91% of the patients in all blood types received ES transfusion before the pandemic, it was 85% in all blood types during the pandemic. FFP was transfused to 14.3% - 25.0% of the patients in all blood types before the pandemic, and this range appeared between 14.3% and 35.7% during the pandemic. Finally, while the patients in all blood types were recruited to PPS transfusion up to 10.6% before the pandemic, this rate was up to 16.7% during the pandemic (**Table 3**).

Table 2. Distribution of the patients receiving ES, FFP, and PPS transfusions in both periods by age and sex

Transfusion Product	Erythrocyte Suspension (ES)		Fresh Frozen Plasma (FFP)		Pooled platelet suspensions (PPS)	
n: Number of Patients %: Percentage	Pre-pandemic (n %)	Mid-pandemic (n %)	Pre-pandemic (n %)	Mid-pandemic (n %)	Pre-pandemic (n %)	Mid-pandemic (n %)
Age						
18-30	38 (97.4%)	15 (83.3%)	8 (20.5%)	7 (38.9%)	1 (2.6%)	0 (0.0%)
31-50	73 (93.6%)	48 (87.3%)	19 (24.4%)	14 (25.5%)	7 (9.0%)	6 (10.9%)
51-70	199 (95.2%)	120 (89.6%)	32 (15.3%)	38 (28.4%)	14 (6.7%)	15 (11.2%)
>70	383 (91.0%)	307 (91.4%)	86 (20.4%)	59 (17.6%)	43 (10.2%)	37 (%11.0)
Sex						
Female	420 (92.5%)	271 (90.7%)	86 (18.9%)	60 (20.1%)	36 (7.9%)	31 (10.4%)
Male	273(3.2%)	219(9.4%)	59(20.1%)	58(23.7%)	29(9.9%)	27(7.2%)

Table 3. Distribution of the patients receiving ES, FFP, and PPS in both periods by blood type and numbers of transfusions

Blood Type	Erythrocyte Suspension				Fresh Frozen Plasma				Pooled platelet suspensions (PPS)			
	Pre-pandemic		Mid-pandemic		Pre-pandemic		Mid-pandemic		Pre-pandemic		Mid-pandemic	
	n %	M±SD	n %	M±SD	n %	M±SD	n %	M±SD	n %	M±SD	n %	M±SD
A (Rh+)	285 92.5%	2.59 (±2.18)	204 90.7%	2.92 (±2.37)	54 17.5%	2.52 (±1.69)	49 21.8%	2.35 (±1.63)	28 9.1%	3.14 (±2.97)	21 9.3%	2.52 (±2.09)
A (Rh-)	44 93.6%	2.95 (±2.57)	27 90.7%	2.70 (±1.75)	11 23.4%	3.73 (±1.90)	4 14.3%	2.00 (±0.82)	5 10.6%	2.20 (±0.84)	3 10.7%	1.67 (±0.58)
B (Rh+)	78 94%	2.27 (±1.51)	64 96.4%	2.66 (±2.13)	13 15.7%	3.00 (±3.49)	17 22.7%	2.29 (±1.11)	5 6.0%	1.40 (±0.55)	11 14.7%	2.00 (±1.55)
B (Rh-)	7 100%	2.43 (±2.15)	12 100%	2.08 (±2.23)	1 14.3%	7.00 (-)	2 16.7%	1.50 (±0.71)	0 0%	-	2 16.7%	1.00 (±0.00)
0 (Rh+)	199 92.6%	2.61 (±2.55)	142 91%	3.13 (±2.41)	52 24.2%	3.35 (±3.72)	34 21.8%	2.50 (±2.54)	21 9.8%	3.00 (±2.59)	17 10.9%	2.06 (±1.48)
0 (Rh-)	34 91.9%	2.68 (±2.00)	12 85.7%	3.00 (±2.13)	6 16.2%	6.17 (±7.14)	5 35.7%	2.20 (±0.45)	2 5.4%	5.00 (±1.41)	0 0	-
AB Rh+)	42 93.3%	2.29 (±1.73)	23 85.2%	3.39 (±2.11)	7 15.6%	2.14 (±0.69)	5 18.5%	1.80 (±0.45)	4 8.9%	1.50 (±0.58)	3 11.1%	3.00 (±2.00)
AB (Rh-)	4 100%	1.25 (±0.50)	6 100%	3.50 (±3.51)	1 25%	1.00 (-)	2 33.3%	2.50 (±2.12)	0 0%	-	1 16.7%	1.00 (-)
Total		1775		1459		450		275		185		127

The patient groups (pre-pandemic and mid-pandemic) significantly differed by the number of product units (ES, FFP and PPS) ($p < 0.05$). In terms of blood type, we determined that while the mean number of ES transfusions was higher for all blood types, except for A Rh (-) and B Rh (-), during the pandemic, the patients with A Rh (-) and B Rh (-) received more ES before the pandemic (**Table 3**).

We also investigated blood product transfusions on the patients with confirmed and suspected COVID-19 by sex and age. Accordingly, the groups significantly differed in ES transfusion by age ($p < 0.05$), but it was not the case by sex ($p > 0.05$). Yet, there were no significant differences between the patients with confirmed and suspected COVID-19 in FFP and PPS transfusion by age and sex ($p > 0.05$). Finally, considering the blood types of the COVID-19-positive patients receiving transfusions, we found significant differences between their blood types by blood product ($p < 0.05$). We determined that 17 patients with confirmed COVID-19 received a total of 37 transfusions. Of the 28 ES transfusions on 13 patients, while 10 were for patients with A Rh (+), 2 were for patients with A Rh (-), and 16 were for patients with O Rh (+). Among 7 FFP transfusions on 3 patients, 1 was for a patient with B Rh (+) while 6 were for patients with O Rh (+). Regarding PPS transfusions, 2 were for a patient with O Rh (+) (**Table 4**).

DISCUSSION

In our study, more than half of the patients (56.4% before the pandemic and 61.9% during the pandemic) were over 70 years old, and the distributions were similar for the other age groups. The patients differed significantly by sex ($p < 0.05$). Considering blood types, the majority of the patients were A Rh (+), followed by O Rh (+).

In the literature, there is a growing research interest in blood types. In a study with 2,586 patients infected with COVID-19, the researchers determined the blood types of the patients as follows: 29.93% (A), 41.80% (B), 21.19% (O), and 7.98% (AB), respectively. Moreover, 98.07% of the patients were Rh positive (7).

Table 4. Distribution of the COVID-19-suspected and -positive patients receiving ES, FFP, and PPS in both periods by blood type and numbers of transfusions

Blood Type	Erythrocyte Suspension				Fresh Frozen Plasma				Pooled platelet suspensions (PPS)			
	Suspicious		Positive		Suspicious		Positive		Suspicious		Positive	
	n %	M±SD	n %	M±SD	n %	M±SD	n %	M±SD	n %	M±SD	n %	M±SD
A (Rh+)	25 (100.0%)	2.64 (±1.38)	4 (100.0%)	2.50 (±1.73)	5 (20.0%)	2.00 (±1.00)	0 (0.0%)	-	8 (32.0%)	3.50 (±2.88)	0 (0.0%)	-
A (Rh-)	1 (50.0%)	2.00 (-)	2 (100.0%)	1.00 (±0.00)	1 (50.0%)	1.00 (-)	0 (0.0%)	-	1 (50.0%)	1.00 (-)	0 (0.0%)	-
B (Rh+)	5 (62.5%)	3.60 (±2.41)	0 (0.0%)	-	3 (37.5%)	2.67 (±2.08)	1 (100.0%)	1.00 (-)	3 (37.5%)	2.00 (±1.00)	0 (0.0%)	-
B (Rh-)	1 (100.0%)	9.00 (-)	-	-	0 (0.0%)	-	-	-	1 (100.0%)	1.00 (-)	-	-
0 (Rh+)	11 (73.3%)	4.91 (±4.04)	7 (100.0%)	2.29 (±2.63)	4 (26.7%)	2.00 (±1.41)	2 (28.6%)	3.00 (±1.41)	1 (6.7%)	1.00 (-)	2 (28.6%)	1.00 (±0.00)
0 (Rh-)	-	-	-	-	-	-	-	-	-	-	-	-
AB Rh+)	3 (100.0%)	2.67 (±1.53)	-	-	0 (0.0%)	-	-	-	0 (0.0%)	-	-	-
AB (Rh-)	1 (100.0%)	8.00 (-)	-	-	1 (100.0%)	4.00 (-)	-	-	0 (0.0%)	-	-	-
Total		165		28		31		7		37		2

The records of blood centers are the primary sources for the most accurate information on the distribution of blood types in countries. In our country, a recent study showed that, among the donors applying to a blood center, 42.84% were A (+), 32.67% were O, 16.46% were B, and 8.03% were AB (8). In our study, we found that 41.4% of those receiving blood transfusions before and during the pandemic were A Rh (+), which is rather close to the finding of the abovementioned study. They were followed by the patients with O Rh (+) at the rates of 28.8% before the pandemic and 28.7% during the pandemic. J. Torabizade Maatoghi et al. (9) examined the blood types of 29,922 donors from their blood center records and found that the majority of the donors were O (40.21%), followed by A.

In their study, Massimo Franchini et al. (10) reported that stated that ABO blood types are distinctive in the formation of many diseases, including cardiovascular diseases and malignancies, which may reinforce the importance of blood types and blood transfusion in diseases. Therefore, considering that an unknown disease, such as COVID-19, has been fought recently, we believe that physicians should reconsider the issue of blood transfusion decision, supply, and application.

Yalaoui S. et al. (11) compared the phenotypes of the blood types of 51 COVID-19 patients and 1,506 non-COVID 19 patients. As a result, they found that the prevalence of blood type A was high in both groups, which is consistent with our study.

Boudin L. et al. (12) examined the relationship between blood type and COVID-19 in young and healthy 1,769 crew members quarantined due to COVID-19 exposure. The results revealed that young adults actually were not at more or less risk for SARS-CoV-2 by blood type.

Simon J Stanworth et al. (13) compiled several studies on this subject and attempted to establish a protocol on the use of blood and blood products. In this review, the authors concluded that a decrease in the use of erythrocytes caused an increase in the use of plasma. On the other hand, the use of platelets was stated as a poor prognostic factor of the course of COVID-19. However, this study supported the view that the work in blood centers would be difficult due to a decrease in blood donations. Pal S. et al. (14) compared the transfusions in their hospital in the first five months of 2020. Although there were significant reductions in the number of patients requiring transfusion (39.69%) thanks to strict COVID-19 measures, they also witnessed a considerable decrease in the number of red blood cell products used (46.41%) and the number of fresh frozen plasma units and platelet concentrates (30%).

In a study with more than 31,100 samples, it was found that blood type A may be more susceptible to COVID-19, while blood type O may be less susceptible to COVID-19 (15). In another study, the pooled frequencies of blood types A, B, O, and AB among individuals infected with COVID-19 were reported as 36.22%, 24.99%, 29.67%, and 9.29%, respectively (16). In their study, Li J et al. (17) recommended that people with blood type A should strengthen their immune to reduce the risk of infection and that people with blood type O should not underestimate the virus and take precautions to avoid the risk of infection.

Although blood type A is more common in our country, we concluded that the CoVID-19 patients with blood type O needed transfusions the most, which overlaps the findings suggesting no association between blood type and the COVID-19 disease.

Convalescent immune plasma is often used in the treatment of patients with COVID-19 (18,19). However, we only investigated plasma used for reasons such as bleeding disorders, disseminated intravascular coagulation, and drug-induced bleeding (20). Our findings showed that there was no significant difference in the amount of plasma used for the abovementioned reasons before and during the pandemic, which implies that COVID-19 does not cause an increase in plasma use, except for convalescent plasma.

There are studies showing that there may be thrombocytopenia in the COVID-19 disease, which is associated with the severity of the disease (21). Marcos S.Z et al. (22) determined that the relationship between COVID-19 and thrombocytopenia was high in blood type B while it was low in blood type O. Based on our records, we found that blood type A platelets were the most needed platelets in PPS transfusions, followed by blood type O platelets. Moreover, the COVID-19 patients needing blood transfussions received PPS transfusions the most.

CONCLUSION

Overall, we interestingly concluded that blood products of blood type O were more prevalently used for COVID-19 patients, although general transfusions often required the products of blood type A which was determined as the most common blood type in our study. The modern world is more likely to encounter further pandemics in the future. We think that each region should evaluate its own centers.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Research Ethics Committee (Date: 14.12.2020, Decision No: 2020-KAEK-143-11).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507–13.
2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. HC. JAMA 2020; 324: 782-93.
3. Mollison PL, Engelfriet P. Blood transfusion. Semin Hematol 1999; 36: 48-58.
4. Kasanga M, Mudenda S, Gondwe T, Chileshe M, Solochi B, Wu J. Impact of COVID-19 on blood donation and transfusion services at Lusaka provincial blood transfusion centre, Zambia. Pan Afr Med J 2020; 35: 74.
5. Mohammadi S, Yazdi SMT, Eshghi P, Norooznezhad AH. Coronavirus disease 2019 (COVID-19) and decrease in blood donation: experience of Iranian Blood Transfusion Organization (IBTO). Vox Sang 2020; 115: 595-6.
6. Hof L, Choorapoikayil S, Meybohm P, Zacharowski K. Patient blood management in intensive care patients. Curr Opin Crit Care 2021; 27: 709-16.
7. Rana R, Ranjan V, Kumar N. Association of ABO and Rh blood group in susceptibility, severity, and mortality of coronavirus disease 2019: a hospital-based study from Delhi, India. Front Cell Infect Microbiol 2021: 2; 11: 767771.
8. Koçtekin B. Antalya Eğitim ve Araştırma Hastanesi Transfüzyon Merkezi'ne başvuran donörlerde ABO ve Rhesus (Rh) kan grupları dağılımının araştırılması. Mersin Üniv Saglık Bilim Derg 2020; 13: 395-403.
9. Maatoghi JT, Paridar M, Shoushtari MM, et al. Distribution of ABO blood groups and rhesus factor in a large scale study of different cities and ethnicities in Khuzestan province, Iran. Egypt J Med Human Gen 2016; 17: 105–9.
10. Franchini M, Liumbruno GM. ABO blood group: old dogma, new perspectives. Clin Chem Lab Med 2013; 51: 1545-53.
11. Yalaoui S, Fakhfakh R, Tritar F, et al. ABO blood groups and risk of COVID-19. Tunis Med 2020; 98: 888-91.
12. Boudin L, Janvier F, Bylicki O, Dutasta F. ABO blood groups are not associated with the risk of acquiring SARS-CoV-2 infection in young adults. Haematologica 2020; 105: 2841–3.
13. Stanworth SJ, New HV, Apelseth TO, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. Lancet Haematol 2020; 7: 756-64.
14. Pál S, Réger B, Kiss T. et al. Effect of SARS-CoV-2 pandemic on blood product usage at the University of Pécs. Orv Hetil 2021; 162: 1717-23.
15. Wu BB, Gu DZ, Yu JN, Yang J, Wang-Qin S. Association between ABO blood groups and COVID-19 infection, severity and demise: a systematic review and meta-analysis. Infect Genet Evol 2020; 84: 104485.
16. Pourali F, Afshari M, Alizadeh-Navaei R, Javidnia J, Moosazadeh M, Hessami A. Relationship between blood group and risk of infection and death in COVID-19: a live meta-analysis. New Microbes New Infect 2020; 37: 100743.
17. Li J, Wang X, Chen J, Cai Y, Deng A, Yang M Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol 2020; 190: 24-7.
18. Brown BL, McCullough J. Treatment for emerging viruses: convalescent plasma and COVID-19.Transfus Apher Sci 2020; 59: 102790.
19. Cesilia C, Ridar E, Suryawan N, Nataprawira HM. Convalescent plasma therapy in obese severe COVID-19 adolescents: Two cases report. Ann Med Surg (Lond) 2021; 72: 103084.
20. Farrugia A, Robert P. Plasma protein therapies: current and future perspectives. Best Pract Res Clin Haematol 2006; 19: 243-58.

21. Lippi G, Plebani M , Henry BM . Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta 2020; 506: 145-8.

22. Marcos SZ, Antelo ML , Galbete A, Etayo M, Ongay E , Garcia-Erce AJ. Infection and thrombosis associated with COVID-19: Possible role of the ABO blood group. Med Clin (Barc) 2020; 155: 340-3.

Original Article

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The prevalence of anemia in elderly patients: a cross-sectional study

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ABSTRACT

Introduction: As the elderly population continues to increase, physiological changes and pathological conditions in old age have started to attract more attention. Anemia is a common public health problem in both developed and developing countries. Many studies have emphasized the negative effects of anemia on poor physical performance, susceptibility to falls, impaired cognitive function and death in the elderly. Considering the classification of anemia, a substantial amount of unexplained anemia in the elderly population raises the question of whether this is a natural consequence of aging. Our aim in this study is to reveal the frequency of anemia in the geriatric population and to classification.

Material and Method: This retrospective cohort study was conducted with the evaluation of patients admitted to the internal medicine outpatient clinic of a secondary state hospital in Ankara. All patients over the age of 65 who applied to the internal medicine outpatient clinic with different complaints between December 2020 and September 2021 and had a hemogram test were evaluated for eligibility for the study.

Results: Anemia was present in 103 of 1210 patients over 65 years of age included in our study. In our study group, the frequency of anemia was 8.5%. The median age of patients with anemia was 73 (65-93) years, and 60.1% (n=62) of these patients were women. The number of patients with at least one comorbidity was 74 (71.8%). The most common type of anemia in patients with anemia was iron deficiency anemia (n=47, 45.6%). Anemia of chronic disease (n=16, 15.5%) was the second most common anemia, and anemia due to vitamin b12 deficiency (n=4, 3.8%) and folic acid deficiency (n=3, 2.9%) was less common. The rate of unexplained anemia was 27.2% (n=28).

Conclusion: It was revealed in our study that anemia is a common health problem in elderly patients in our society, and that unexplained anemia can be seen at a substantial rate. The prevalence of anemia of approximately 10% in our study gives the message that anemia is an important public health problem for the elderly population and that health care providers should be careful in terms of preventive and therapeutic measures.

Keywords: Anemia, elderly, unexplained anemia

INTRODUCTION

Traditionally, patients aged 65 and over are defined as elderly (1). In the report published by the World Health Organization (WHO), it has been reported that the elderly population is increasing gradually, and it is estimated that 10-15% of the entire world population will consist of people over the age of 65 by 2030 (2). It is seen that the situation in our country is similar to that of the world. According to the data of the Turkish Statistical Institute (TUIK) for 2020, the elderly population in Turkey is 9.5% of the entire population, and 44.2% of this population consists of men and 55.8% women (3).

Biologically, aging is the accumulation of a series of damage that occurs at the molecular and cellular level. This damage leads to a decrease in physiological capacity over the years and an increase in the risk of various diseases. In this physiological process, which includes all organs and systems, it is of great importance to distinguish changes due to normal aging from pathological ones (4).

Anemia is a common public health problem in both developed and developing countries. Many studies have emphasized the negative effects of anemia on poor physical performance, susceptibility to falls, impaired cognitive function and death in the elderly (5-8). While

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anemia was detected in approximately 11% of the population over 65 years of age in the National Health and Nutrition Research Study (NHANES III), this rate increased to 26.1% in men and 20.1% in women over the age of 85 in the same study (9).

The most common causes of anemia etiology in the geriatric population are nutritional deficiencies (iron deficiency, vitamin B12 deficiency, folate deficiency) and chronic diseases (chronic kidney disease, inflammatory diseases), and there is a significant number of patients whose underlying cause cannot be explained. Anemia in this group is called unexplained anemia (UA) (10). UA appears to be the mainstay of the debate on whether anemia is a natural consequence of aging.

Our aim in this study is to reveal the frequency of anemia in the geriatric population and to investigate its etiology, which is an extremely important public health problem and can lead to hospitalization and loss of function if not treated appropriately.

MATERIAL AND METHOD

This retrospective cohort study was conducted with the evaluation of patients admitted to the internal medicine outpatient clinic of a secondary state hospital in Ankara. The study was approved by the Ethics Committee of the University of Health Sciences, Ankara Oncology Training and Research Hospital Ethics Committee (Date: 28.07.2021, Decision No: 2021-07/1311). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

All patients over the age of 65 who applied to the internal medicine outpatient clinic with different complaints between December 2020 and September 2021 and had a hemogram test were evaluated for eligibility for the study. Patients whose medical information could be accessed through a manual or electronic patient registration system were included in the study. Those under the age of 65 and with incomplete medical information were excluded from the study. According to the WHO definition, anemia is defined as a hemoglobin level of <13 g/dl in men and <12 g/dl in women. Only hemogram test results were recorded in non-anemic patients. In patients with anemia, demographic characteristics, chronic diseases and, etiological laboratory parameters that may be associated with anemia (MCV, MCHC, serum iron, iron binding capacity, ferritin, folate, vitamin B12 level, LDH, sedimentation, CRP, GFR, TSH, free T4) were recorded retrospectively and transferrin saturations were calculated.

As accepted in national and international guidelines, ferritin <12 mg/l and transferrin saturation <15% were defined as iron deficiency anemia, vitamin B12 level <200 pg/ml as vitamin B12 deficiency anemia, and folic acid level <3 ng/ml as folate deficiency anemia (11-13). Anemia with high levels of inflammatory markers (such as C-reactive protein) while iron stores are normal (transferrin saturation >15%, serum ferritin >12 ng/ml) and serum iron level is low (<60 g/dL) is defined as anemia of chronic disease (14). The type of anemia in which the etiology of anemia could not be explained and there was no nutritional deficiency or anemia of chronic disease was defined as unexplained anemia (9).

The primary endpoint of the study was to determine the frequency of anemia in patients aged 65 and over. The secondary endpoint was to determine the demographic characteristics and anemia subtypes of patients with anemia. Data were analyzed using the SPSS 23.0 (SPSS Inc., Chicago, IL, USA) program. Kolmogorov-Smirnov test was used to evaluate the distribution of data. The distribution of normal data was reported as mean ± standard deviation (SD), data with non-normal distribution and non-parametric data were reported as the median.

RESULTS

Anemia was present in 103 of 1210 patients over 65 years of age included in our study. In our study group, the frequency of anemia in geriatric patients was 8.5%. The median age of patients with anemia was 73 (65-93) years, and 60.1% (n=62) of these patients were women. The number of patients with at least one comorbidity was 74 (71.8%). The most common comorbid diseases were diabetes mellitus (n=35, 33.9%), hypertension (n=34, 33%) and coronary artery disease (n=21, 20.3%). Eight patients (7.7%) had chronic kidney disease, 7 (6.7%) patients thyroiditis, 6 (5.8%) patients malignancy, and 4 (3.8%) patients chronic obstructive pulmonary disease. Patient characteristics are shown in **Table 1**.

Table 1. Demographic characteristics patients with anemia

Variables	(n=103)	%
Age (years), Median (min-max)	73 (65-93)	
Gender		
Male	41	39.8
Female	62	60.1
Comorbidites		
Diabetes mellitus	35	33.9
Hypertansion	34	33.0
Coronary artery disease	21	20.3
Chronic kidney disease	8	7.7
Thyroidit	7	6.7
Chronic obstructive pulmonary disease	6	5.8
Anemia subtype		
Iron-deficiency anemia (IDA)	47	45.6
Vitamin B12 deficiency anemia	4	3.8
Folate deficiency anemia	3	2.9
Chronic disease anemia	16	15.5
Unexplained anemia	28	27.2
Mixed anemia (IDA/Vit B12 def.)	5	4.8

The most common type of anemia in patients with anemia was iron deficiency anemia (n=47, 45.6%). Anemia of chronic disease (n=16, 15.5%) was the second most common anemia, and anemia due to vitamin b12 deficiency (n=4, 3.8%) and folic acid deficiency (n=3, 2.9%) was less common. The rate of unexplained anemia was 27.2% (n=28).

The median hemoglobin value of the patients with anemia was 10.3 g/dl. Median white blood cell and platelet counts were normal. Median ferritin level was close to the lower limit, and parallel to this, transferrin saturation was also below normal. Median folic acid and vitamin B12 levels were also in the normal range. Anemia-related laboratory parameters of the patients are shown in **Table 2**.

Table 2. Laboratory values of patients with anemia

Variable	Median	Min-max	Normal
Hemoglobin (gr/dl)	10.3	5.0-12.9	12-17
MCV (fl)	82.0	59.0-119.0	80-100
White blood cells (/µl)	6800	3390-14800	4500-11000
Platellet (10^3/µl)	275	102-544	150-450
Ferritin (µg/l)	20.0	1.0-578	11-307
Folic asid (ng/ml)	7.0	2.6-44.0	2.7-17.0
Vitamin B12 (pg/ml)	284.0	3.8-1933	160-950
Total Bilirubin (mg/dl)	0.5	0.3-3.8	< 1.2
Lactate dehydrogenase (U/l)	201	126-2011	140-280
Transferrin saturation (%)	%15	%2-%50	15-50
C-reactive protein (mg/l)	5.2	0.1-98	< 10

DISCUSSION

In this study, which screened more than 1200 patients and aimed to investigate the frequency and etiology of anemia in the geriatric population, the frequency of anemia in patients over 65 years of age was found to be 8.5%. While iron deficiency anemia was present in approximately half of the patients with anemia, it was remarkable that unexplained anemia constituted approximately 27% of the cases.

With the increase in the elderly population in the world, it is more important to distinguish the physiological changes that occur with old age from the pathological ones (15,16). It has been reported that anemia, the negative effects of which have been clearly demonstrated in elderly patients, are seen at rates of up to 60% in the geriatric population in some countries (17,18). When evaluated etiologically, it was observed that up to 40% of these patients had unexplained anemia (9,19-20). This raises the question of whether anemia is a natural consequence of aging.

One of the earliest epidemiological studies investigating anemia in the elderly population was conducted in Minnesota in the 1990s. In this study, which included approximately 600 patients, the prevalence of anemia was found to be 9% in males and 7% in females over the age of 65. While patients with anemia due to acute bleeding constitute half of the whole group, it has been reported that anemia of unknown cause constitutes 16% of the group (19).

One of the most comprehensive and representative of the whole population studies on the prevalence of anemia in elderly patients has been reported from the US. Based on the data obtained from the population-based NHANES III study, the prevalence of anemia in the US population aged 65 and over was determined as 10.2%. Based on these results from approximately 4,200 patients in the geriatric population, one-third of patients had nutritional anemia (iron deficiency, vitamin B12 or folate deficiency), and one-third had anemia of chronic disease. The rate of unexplained anemia was 33% (9). The most important limitation of this study was the inability to perform all diagnostic tests for the etiology of anemia. This may have caused the unexplained anemia rate to be higher than it actually is.

In a population-based prospective observational study conducted in Italy, approximately 9000 elderly patients were investigated for anemia. The incidence of anemia in patients over 65 years of age has been determined as 11%. It has been reported that the frequency of anemia gradually increases with age and reaches 40% over the age of 90. Anemia of chronic disease, thalassemia, and renal failure were the most common mild anemia types, whereas the cause of anemia could not be explained in 26.4% of the cases (21).

In a large cross-sectional study, which retrospectively evaluated approximately 20,000 patients who applied to outpatient clinics in Austria, the frequency of anemia was determined as 21%. In the analysis performed for anemia classification, it was reported that approximately 60% of the cases had high inflammatory parameters, approximately half of them had renal insufficiency and 20% had nutritional deficiency (22).

Another study with a similar design to our study was reported from Poland in 2020. The frequency of anemia was found to be 17% in approximately 1000 patients over the age of 60 who were investigated for anemia in the primary health care center. Remarkably, in this study, 28% of patients with anemia were found to have unexplained anemia. However, the fact that all hematological diagnostic tests could not be performed in 81% of the patients was an important limitation of this study (23).

One of the most comprehensive studies investigating the frequency of anemia in the elderly population in our country was carried out by evaluating hospitalized patients retrospectively (24). Anemia prevalence was found to be 76% in 715 patients hospitalized in the

internal medicine clinic. Considering the causes of this high anemia rate, it was reported that approximately half of the patients had anemia associated with inflammation, and one third of the patients had anemia due to chronic renal failure. This has been interpreted as the results obtained in hospitalized patients cannot be generalized to the whole population. In another study conducted in our region, which included a sufficient number of patients, the frequency of anemia was reported as 7% in approximately 800 patients over the age of 60 who applied to the outpatient clinic (25). However, in this study, the presence of chronic diseases was defined as an exclusion criterion. This allowed the investigation of only nutritional anemia.

As seen in these studies (9,19-25), which we have mentioned so far, investigating the frequency of anemia in the elderly and trying to classify anemia, the rate of anemia varies between 7% and 21%. In our experience, which is one of the most comprehensive studies on this subject in Turkish society, this rate was found to be 8.5%. The rate of anemia in our elderly patients can be considered relatively low compared to some societies. The fact that more risky groups were screened in terms of anemia in some studies may have caused the incidence of anemia to appear higher. Considering the anemia classification in these studies, it has been reported that nutritional anemia and anemia of chronic disease are generally in the first place among the elderly population, but unexplained anemia is seen at rates of up to 40%. Similarly, nutritional anemia ranked first in our study, and the cause of anemia could not be explained in about a quarter of our patients. As in all studies, the lack of advanced tests such as bone marrow biopsy for the etiology of anemia was thought to be the reason for the unexplained anemia rate to appear so high in our study. It should be kept in mind that some of the unexplained anemia will be diagnosed as myelodysplastic syndrome in the long term.

The most important limitation of our study was its retrospective nature. This situation led to the conclusion that the etiology of anemia was not clearly investigated in some of the patients. Evaluation of patients who applied to the internal medicine outpatient clinic for any reason may also mean that there is a relatively bias in patient selection. Because, in daily practice, some of the patients who apply to the internal medicine outpatient clinic apply to the outpatient clinic due to comoborbid diseases. Since the frequency of anemia is expected to be higher in this group than in the whole population, this can be seen as a limiting factor in terms of reflecting the results obtained for the whole population. However, our study appears to be an impressive real-life analysis involving a fairly large geriatric population of approximately 1200 patients.

CONCLUSION

It was revealed in our study that anemia is a common health problem in elderly patients in our society, and that unexplained anemia can be seen at a substantial rate in addition to anemia due to nutritional causes and chronic diseases. The prevalence of anemia of approximately 10% in our study gives the message that anemia is an important public health problem for the elderly population and that health care providers should be careful in terms of preventive and therapeutic measures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences, Ankara Oncology Training and Research Hospital Ethics Committee (Date: 28.07.2021, Decision No:2021-07/1311).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly." Geriatr Gerontol Int 2006; 6: 149-58.
2. World Health Organization (WHO), https://www.who.int/ageing/publications/global_health.pdf, October 2011.
3. Türkiye İstatistik Kurumu (TUIK), https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Yaslilar-2020-37227, 18 March 2021.
4. Bilir N. Yaşlılık tanımı, yaşlılık kavramı, epidemiyolojik özellikler. yaşlılık ve solunum hastalıkları: TÜSAD Eğitim Kitapları Serisi; 2018: 13-31.
5. Penninx BW, Pluijm SM, Lips P, et al. Late-life anemia is associated with increased risk of recurrent falls. J Am Geriatr Soc 2005; 53: 2106-11.
6. Chaves PH, Carlson MC, Ferrucci L, Guralnik JM, Semba R, Fried LP. Association between mild anemia and executive function impairment in community-dwelling older women: The Women's Health and Aging Study II. J Am Geriatr Soc 2006; 54: 1429-35.
7. Denny SD, Kuchibhatla MN, Cohen HJ. Impact of anemia on mortality, cognition, and function in community-dwelling elderly. Am J Med 2006; 119: 327-34.
8. Penninx BW, Pahor M, Cesari M, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. J Am Geriatr Soc 2004; 52: 719-24.
9. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood 2004; 104: 2263-68.

10. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. Clin Interv Aging 2014; 9: 1187-96.
11. Camaschella C. Iron deficiency. Blood 2019; 133: 30–9.
12. Oymak Y, İlhan G. B12 vitamin eksikliği tanı ve tedavi klavuzu. Eritrosit hastalıkları ve hemogoblobin bozuklukları tanı ve tedavi klavuzu, Türk Hematoloi Derneği 2019: 1-10.
13. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol 2014; 166: 496-513.
14. Paula G. Fraenkel; Understanding anemia of chronic disease. Hematology Am Soc Hematol Educ Program 2015; 2015: 14–8.
15. Penninx BWJH, Pahor M, Woodman RC, Guralnik JM. Anemia in old age is associated with increased mortality and hospitalization. J Gerontol A Biol Sci Med Sci 2006; 61: 474-9.
16. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. Blood 2006; 107: 3841-6.
17. Zakai NA, Katz R, Hirsch C, et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovascular Health Study. Arch Intern Med 2005; 165: 2214-20.
18. Beghé C, Wilson A, Ershler WB. Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. Am J Med 2004; 116: 3S-10S.
19. Anía BJ, Suman VJ, Fairbanks VF, Rademacher DM, Melton LJ. Incidence of anemia in older people: an epidemiologic study in a well defined population. J Am Geriatr Soc 1997; 45: 825-31.
20. Artz AS, Thirman MJ. Unexplained anemia predominates despite an intensive evaluation in a racially diverse cohort of older adults from a referral anemia clinic. J Gerontol A Biol Sci Med Sci 2011; 66: 925-32.
21. Tettamanti M, Lucca U, Gandini F, et al. Prevalence, incidence and types of mild anemia in the elderly: the "Health and Anemia" population-based study. Haematologica 2010; 95: 1849-56.
22. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. Clin Interv Aging. 2014; 9: 1187-96.
23. Michalak SS, Rupa-Matysek J, Hus I, Gil L. Unexplained anemia in the elderly - a real life analysis of 981 patients. Arch Med Sci 2019; 16: 834-41.
24. Taşar PT, Şahin S, Emgin Ö, et al. Evaluation of anemia in geriatric inpatients. Tepecik Eğit Hast Derg 2015; 25: 43-8.
25. Yildirim T, Yalcin A, Atmis V, et al. The prevalence of anemia, iron, vitamin B12, and folic acid deficiencies in community dwelling elderly in Ankara, Turkey. Arch Gerontol Geriatr 2015; 60: 344-8.

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Does prior uterine surgery increase the risks of uterine leiomyoma and adenomyosis? a retrospective study

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ABSTRACT

Aim: Women frequently undergo obstetric and gynecologic surgeries throughout their life, and the two common gynecologic conditions are uterine leiomyoma (UL) and adenomyosis. This study aims to investigate the relationship between the presence and the types of prior uterine surgery and the risks of developing UL and adenomyosis.

Material and Method: This study is a single-center eleven-year cross-sectional study, in which we studied the effects of previous uterine surgery on developing UL and adenomyosis in patients who underwent hysterectomy for any indication in our hospital between 01/01/2004 and 31/12/2014.

Results: During the time period, 1299 eligible patients were included in the study. The median age was 49.0 years and the study population was mostly consisted of multigravid women. The overall prevalence of UL was 61.9% and the overall prevalence of adenomyosis was 18.3%.In the univariate analysis of patient characteristics for UL, age, gravida and parity were found as statistically significant protective factors for UL (OR [95.0% CI]: 0.92 [0.91-0.93], 0.91 [0.88-0.95], 0.88 [0.83-0.93], respectively). On the other hand, women who underwent previous any uterine surgery had 1.28 folded (95.0% CI: 1.02-1.61) risk for UL. However, we found that only undergoing myomectomy statistically significantly increased the risk of UL (OR [95.0% CI]: 8.59 [2.62-27.91]) among the types of uterine surgery. In the multivariate model, the protective effect of age remained (adjusted OR [95.0% CI]: 0.92 [0.91-0.94]), and the risk-increasing effect of having previous myomectomy dropped slightly with retaining its statistical significance (adjusted OR [95.0% CI]: 5.87 [1.78-19.41]). We also conducted similar analysis for adenomyosis, and we found that gravida was a risk factor (OR [95.0% CI]: 1.06 [1.01-1.12]), conversely to its risk-decreasing effect for UL. Also, women who had a history of any uterine surgery had 1.42 folded (95.0% CI: 1.07-1.88), and women who had a history of D&C had 1.62 folded (95.0% CI: 1.02-1.61) risk adenomyosis. In the multivariate model for the risk of adenomyosis, the risk-increasing effects of the gravida and the history of D&C decreased very slightly with saving their statistical significances (adjusted OR [95.0% CI]: 1.06 [1.01-1.12], 1.44 [1.07-1.95], respectively).

Conclusion: According to our findings, the frequency of adenomyosis is higher but, the frequency of UL is compatible with the literature. Patients, who underwent uterine surgery previously, diagnosed with adenomyosis and UL more than the others who did not, but this seems to be a correlation rather than a causative association.

Keywords: Uterine surgery, hysterectomy, uterine leiomyoma, adenomyosis.

INTRODUCTION

Uterine leiomyoma (UL) is the most prevalent tumor in women, with estimates indicating they impact over 70% of women when they reach menopause (1, 2). It is predicted to be clinically evident in 25% of women of reproductive age and induce severe enough symptoms to warrant treatment in around 25% of women with ULs (3).Even though many studies on the epidemiology of ULs have been published, estimates of the incidence and prevalence of ULs vary greatly depending on the method of diagnosis, and the population studied; for example, estimates of the incidence of ULs range from 5.4 percent to 77 percent of women of reproductive age, depending on the method of diagnosis and the population studied(4).Furthermore, adenomyosis and UL frequently occur; simultaneous adenomyosis ranges from 15% to 57 percent in hysterectomy tissues of women with UL (5, 6). Age, multiparity, surgical disturbances of the endometrial-myometrial border, increased Follicle-

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stimulating hormone and prolactin levels, smoking habits, and a history of depression are all risk factors for adenomyosis (7,8).

UL prevalence is likely to be underestimated because many women are asymptomatic or acquire symptoms gradually, leaving the sickness undetected (9,10). Because of the uncertain extent and impact of undiscovered ULs, epidemiological statistics and evidence on related factors are skewed to represent severe disease (11). Furthermore, various risk variables, including biological, demographic, reproductive, and lifestyle factors, have been linked to the development of ULs (2). As a result, the true incidence and prevalence of ULs and their global impact on women's health and the role of potential risk factors are unknown at this time. ULs that have been pathologically diagnosed increase in frequency with age, peaking at 50 years old (12), and do not appear before puberty and become less common after menopause. ULs are shown to be 2-3 times more common in black women, but the incidence of ULs is similar in Hispanic, Asian, and White women (12). The lifetime risk for ULs was almost 70% in white women and 80% in black women, and if only clinically significant ULsare included, the incidence reaches 50% in Black women and 25% in White women (13).

In the United States, ULs are the most common reason for hysterectomy (14). The specific pathophysiology of UL formation is unknown(15). To the best of our knowledge, UL formation begins with a single uterine smooth muscle cell (myometrium), which is subsequently followed by deviations from normal cellular division signaling pathways(16). ULs are estrogen-dependent tumors, and, as compared to normal myometrium, they overexpress particular estrogen and progesterone receptors(17). The presence of ectopic endometrium with or without hyperplasia of myometrium characterizes adenomyosis, a myometrial lesion. Adenomyosis is a benign uterine condition characterized by heterotopic endometrial glands and stroma in the myometrium, as well as reactive fibrosis of the myometrium's surrounding smooth muscle cells. A variety of theories have been proposed during the last 80 years to explain how adenomyosis develops. The most widely accepted theory is that adenomyosis is caused by the invagination of the endometrium's basalis into the myometrium. This basalis invagination, according to a second idea, would occur along with the intramyometrial lymphatic system. A third idea proposes that ectopic intramyometrial endometrial tissue initiates a de novo metaplastic process (18). There is no data about that surgery might be a cause of UL and/or adenomyosis. We aimed to investigate the relationship between prior uterine surgery and UL, and adenomyosis, and to evaluate the effects of the type of uterine surgery on the risk of developing these diseases.

MATERIAL AND METHOD

Study Design and Setting

This study was planned retrospectively and was carried out with the decision of Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Date: 14.01.2015, Decision No: 02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This single-center eleven-year cross-sectional study was conducted in tertiary care training and research hospital in Ankara. The Obstetrics and Gynecologic Clinic of our hospital is consisted of 22 experienced obstetrician and gynecologists and residents, and we performed approximately 1200 gynecologic surgeries, 2500 C/S deliveries, and 3500 vaginal deliveries annuall.

Patients and Data

We did not calculate any prior minimum sample size because we had intended to include all eligible patients in the study according to the inclusion and exclusion criteria. The inclusion criteria of the studywere: (1) undergoing hysterectomy for any indication between 01/01/2004 and 31/12/2014, and (2) having the report of pathologic examination of uterine specimens; and the single exclusion criterion is the missing data of the variables of the study which were age, obstetrical and surgical history, and the pathologic examination findings.

We collected the data using Hospital Information Management System (HIMS) which is used almost in all public hospitals in Turkey, and patient files, and contacting with patients via telephone when it would be necessary particularly in some situations such as missing data in an essential patient information. Participants were determined by searching the terms “leiomyoma”, “myoma uteri” and “adenomyosis” via HIMS.

Variables and Outcomes

Patients' demographics, obstetrical and clinical features, surgical history, and the pathologic examination findings, which are obtained from their pathology reports, were recorded. There are two primary outcomes of this study, which we used to evaluate the effects of patients' surgical features on them. These two primary outcomes are the risk of UL and the risk of adenomyosis in patients included in the study. As stated above, we investigated to how the presence and/or the type of prior uterine surgery affect the risk of developing these two health issues. The secondary outcomesof this study are the prevalence of UL and the prevalence of adenomyosis in hysterectomy patients.

Statistical Analysis

Statistical analyses were done using SPSS v 23 software (SPSS Inc., Chicago, IL, USA). The descriptive statistics were presented as median with interquartile rage (IQR)

for numerical variables and frequency (n) with percentage (%) for categorical variables. The 95% confidence interval (95% CI) was calculated for overall prevalence of UL, and overall prevalence of adenomyosis. Binary logistic regression analyses of patient characteristics were performed to estimate the risks of the presence of dependent variables which were UL and adenomyosis. Then, the Odds ratios (ORs) with 95% CIs were calculated to present the risks of these two diseases. A value of $p<0.05$ was approved as the statistically significance level.

RESULTS

During the time period for data collection that we defined before beginning the study, we reviewed 1400 patients who met the inclusion criteria; thereafter 101 patients were excluded because of missing data, and finally 1299 patients were included in the study. **Table 1** presents demographics, obstetric and medical history, and pathologic findings of the patients. The median age was 49.0 years with an IQR of 45.0-55.0 years. Our study population, in which abortion was rare, was mostly consisted of multigravid women, and the median parity was 2.0 with an IQR of 1.0-4.0. According to the pathologic examination, there were UL in 657 (50.6%) patients, and adenomyosis in 96 patients (7.4%) purely; however, UL accompanied with adenomyosis in 147 patients (11.3%). The overall prevalence of UL was 61.9% and the overall prevalence of adenomyosis was 18.3% (**Table 1**).

In the univariate analysis of patient characteristics for UL, age, gravida and parity were found as statistically significant protective factors for developing UL (OR [95.0% CI]: 0.92 [0.91-0.93], 0.91 [0.88-0.95], 0.88 [0.83-0.93], respectively). On the other hand, women who underwent previous any uterine surgery had 1.28 folded (95.0% CI: 1.02-1.61) risk for UL when compared to the patients who did not undergo. However, we found that only undergoing myomectomy statistically significantly increased the risk of UL (OR [95.0% CI]: 8.59 [2.62-27.91]) among the types of uterine surgery. And this risk was also higher than having a prior any uterine surgery (**Table 2**).

Table 1. Demographics and clinical features of the patients

Characteristics (n=1299)	
Age (years), median (IQR)	49.0 (45.0-55.0)
Gravida, median (IQR)	4.0 (2.0-5.0)
Parity, median (IQR)	2.0 (1.0-4.0)
Aborts, median (IQR)	0.0 (0.0-1.0)
Surgical history	
Previous C/S, n (%)	123 (9.5)
Previous myomectomy, n (%)	43 (3.3)
Previous D&C, n (%)	472 (36.3)
Previous hysteroscopy, n (%)	2 (0.2)
Pathological findings	
Pure UL, n (%)	657 (50.6)
Pure adenomyosis, n (%)	96 (7.4)
UL accompanied with adenomyosis, n (%)	147 (11.3)
Overall prevalence (95% CI)	
UL	61.9% (59.3%-64.5%)
Adenomyosis	18.3% (16.6%-20.8%)

We also performed a multivariate logistic regression analysis with the factors that were statistically significantly related the risk of developing UL. We did not include the parity because of its high correlation with the gravida, and, similarly, the presence of previous any uterine surgery because of its high-level correlation with previous myomectomy. In the multivariate model, the protective effect of age remained (adjusted OR [95.0% CI]: 0.92 [0.91-0.94]), and the risk-increasing effect of having previous myomectomy dropped slightly with retaining its statistical significance (adjusted OR [95.0% CI]: 5.87 [1.78-19.41]); however, the association between gravida and the risk of UL lost its statistical significance (**Table 2**).

We also repeated the univariate analysis of patient characteristics for adenomyosis, and we found that gravida was a risk factor for adenomyosis (OR [95.0% CI]: 1.06 [1.01-1.12]), conversely to its risk-decreasing effect for UL. Also, women who had a history of any uterine surgery had 1.42 folded (95.0% CI: 1.07-1.88), and women who had a history of D&C had 1.62 folded (95.0% CI: 1.02-1.61) risk for developing adenomyosis when compared to the females who did not undergo (**Table 3**).

Table 2. Univariate and multivariate logistic regression analyses of patient characteristics for UL

Factors	**Univariate Analysis**			**Multivariate Analysis**		
	OR	**95% CI**	**p**	**Adjusted OR**	**95% CI**	**p**
Age (years)	0.92	0.91-0.93	<0.001	0.92	0.91-0.94	<0.001
Gravida (numbers)	0.91	0.88-0.95	<0.001	0.98	0.93-1.02	0.336
Parity (numbers)	0.88	0.83-0.93	<0.001			
Abortus (numbers)	0.93	0.82-1.07	0.311			
Previous (any) uterine surgery	1.28	1.02-1.61	0.032			
Previous C/S	0.99	0.68-1.46	0.980			
Previous myomectomy	8.59	2.62-27.91	<0.001	5.87	1.78-19.41	0.004
Previous D&C	1.10	0.87-1.39	0.415			

Table 3. Univariate and multivariate logistic regression analyses of patient characteristics for adenomyosis

Factors	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	Adjusted OR	95% CI	p
Age (years)	1.00	0.98-1.01	0.669			
Gravida (numbers)	1.08	1.03-1.14	0.001	1.06	1.01-1.12	0.031
Parity (numbers)	1.06	0.99-1.12	0.103			
Abortus (numbers)	1.08	0.92-1.27	0.348			
Previous (any) uterine surgery	1.42	1.07-1.88	0.014			
Previous C/S	0.83	0.50-1.37	0.465			
Previous myomectomy	0.44	0.15-1.23	0.118			
Previous D&C	1.62	1.22-2.15	0.001	1.44	1.07-1.95	0.017

After evaluating the characteristics that showed a statistically significant impact on developing adenomyosis, we performed a multivariate logistic regression analysis. Similarly, in the multivariate model that we set to analyze the factors for the risk of UL, we preferred only one factor among the factors that showed high correlation. In the multivariate model for the risk of adenomyosis, the risk-increasing effects of the gravida and the history of D&C decreased very slightly with saving their statistical significances (adjusted OR [95.0% CI]: 1.06 [1.01-1.12], 1.44 [1.07-1.95], respectively) (**Table 3**).

DISCUSSION

The present study has shown that patients with UL are older, has higher gravida, parity, also previous any uterine surgery includes myomectomy. We have shown that patients with adenomyosis are most likely to have any uterine surgery also D&C and gravida also tend to end up with uterine surgery. In a study with 549 patients, researchers discovered that the incidence of adenomyosis ranged from 10% to 18% depending on the criteria used, and that there was no significant link between adenomyosis and uterine surgery, such as previous cesarean section, myomectomy, or dilation and curettage (D&C) (19). Another publication studied the pathologic species of 873 patients and found that 41.7 percent of them had adenomyosis. Adenomyosis and previous uterine surgery, such as cesarean section, myomectomy, D&C, and dilation and evacuation (D&E), were found to have no significant relationship in this study; however, uterine surgery (caesarian section, myomectomy, D&C, and D&E) is one of the most common factors associated with the incidence of adenomyosis (20). Our data has shown that 61.9% of patients have UL, and %18.3 of patients have adenomyosis. Literature has revealed that ULs occur in more than 70% of women based on ultrasonography screening studies and pathology data (21). According to the data of Yu et al. (22), they studied 1,185,855 women during the ten years, 3,425 women received the first diagnosis of adenomyosis and were considered potential incident cases. Our data controversially showed higher incidence.

Several authors define recurrence as the growth of UL left behind during surgery. One study found that the estimated rate of post-operative persistence of ULs was 29% when the myometrium was carefully examined by ultrasound scan six months after surgery (22). Recurrence, on the other hand, is a natural progression of the myometrial illness. Alterations cause the condition in the myometrium cells, such as spontaneous chromosomal rearrangement, responsible for the onset and proliferation of UL growth (23). Because most UL in a myomatous uterus are numerous and many of them measure less than 5 mm, it is difficult to distinguish between recurrence of ULs due to a surgeon's technical error and actual recurrence due to disease progression (24). The Fedele et al. (35), use of routine ultrasound at regular intervals to detect recurrence could have considered tiny ULs, which can be as small as 1 cm in diameter. The true incidence of these small myomatous nuclei in a population without myomatous pathology is unknown, and such small ULs may not be clinically significant. UL is found in more than half of women whose uteri were excised for reasons other than UL, according to Cramer and Patel (25). On the other hand, clinical signs and symptoms are not reliable because they are not unique to ULs (26). Furthermore, the recurrence may occur in a different location than the original, resulting in distinct symptoms. In addition to this, there are also methodological difficulties in the studies investigated fibroid recurrence such as loss to follow up and associated censored data (27). Also, there may be a possibility of sample bias in these studies. For example, most of the patients who lost to follow-up may be those who do not have recurrence and therefore do not come to the clinic. On the other hand, there may actually be uterine leiomyoma recurrence in these patients even if they do not have a symptom. For all these reasons, the true incidence of uterine leiomyoma recurrence is not known exactly and is probably higher than those found in studies.

In our study, we found that any previous uterine surgery increased the risk of uterine leiomyoma recurrence. We found that this risk was actually associated with

previous myomectomy. It seems reasonable to find that the risk of being diagnosed with myoma uteri is high in patients who have undergone myomectomy because the disease tends to recur. However, residual myoma foci is probably the risk factor for new fibroid formation, not the myomectomy. Parity after myomectomy was associated with a decreased rate of UL recurrence, which is consistent with the findings of other studies. Parous women have a reduced risk of UL than nulliparous women, according to epidemiological studies. The discrepancy was attributed to either lower fertility due to UL or a protective impact of pregnancy on UL development by the researchers. In the Caucasian population, however, Stewart et al. discovered that parity after myomectomy increased the incidence of recurrence and the requirement for additional surgery for UL (14). Furthermore, our research revealed an exponential increase in recurrence rate with time, corroborated by previous studies. In literature, it was shown that half of the cases was re-operated and a hysterectomy was performed for one-third of patients in case of leiomyoma recurrence (27). For this reason, patients should be informed in detail about uterine leiomyoma recurrence and possible re-operation. Women should also be advised to complete their families as soon as possible following myomectomy.

Even though adenomyosis is a principal medical diagnosis, there is still much debate over its incidence, origin, concomitant pathology, and clinical manifestations. The 1940 Zaleski hypothesis that the displacement of viable endometrium causes adenomyosis during pregnancy and delivery, as well as recent reports of adenomyosis after endometrial ablation, prompted us to investigate whether prior uterine surgery, such as cesarean delivery, myomectomy, endometrial ablation, D&E, and D&C, is a risk factor for the development of adenomyosis (21, 28, 29). We identified a strong link between adenomyosis and prior uterine surgery in this retrospective analysis. We feel that our findings support the idea that any surgical intervention on the uterus disrupts the endometrial junction, resulting in adenomyosis. Patients with UL and adenomyosis, on the other hand, are more likely to undergo surgery, which could explain why there is such a strong link between surgical treatments and UL and adenomyosis. Thus, uterus surgery appears to raise the risk at first glance. If D&C increases the risk in subgroup analyses while having no effect on other types of surgery, D&C is a marker, not a cause. In other words, patients with adenomyosis tend to relapse and have adenomyosis again, more than patients without adenomyosis. This may cause increased D&C in patients with adenomyosis. This is also possible due to the hereditary predisposition and recurrence of adenomyosis.

Limitations

These investigations, including ours, were retrospective, and we believe that only a prospective study with a set sample size can provide a definitive response to this topic. Such a study may not be feasible due to the length of time that patients must be followed prospectively. We did not examine whether single or many cesarean deliveries in the past contributed to subsequent adenomyosis in our study, but it should be considered in future research. According to studies, the risk of adenomyosis increases following DC. There is no information about the cause of D&C in our study. If there were, we could compare the risks of D&Cs with and without adenomyosis. As a result, we could assess the myomectomy-UL recurrence strategy in this case. We, on the other hand, did not have that opportunity. In other words, myomectomy is only performed when ULs are present, but it can also be done for reasons other than D&C adenomyosis. Another drawback of this retrospective analysis is that data on adenomyosis was collected from post-operative pathology reports; pathologists did not re-examine the specimens for this condition. Adenomyosis is identified more commonly when a thorough histopathologic examination is performed. UL and adenomyosis were also classified, although these patients were not excluded from the UL accompanied with adenomyosis group. The increased occurrence of adenomyosis among women without ULs or with smaller ULs in our study could be due to more thorough examination by pathologists who could not make a histopathologic diagnosis of uterine material otherwise. Finally, important data such as patients' weight, height, age at first menstruation, and alcohol consumption, or size and location of the excised fibroids could not be reached by searching for terms on the system. The fact that these parameters were not included in the study was also determined as an important limitation.

CONCLUSION

According to the literature, there is no link between prior uterine surgery and adenomyosis. There is no information concerning the relationship between UL and past uterus surgery that we are aware of. According to our findings, the frequency of adenomyosis is higher compared to other studies reported. The frequency of UL is compatible with the literature. Patients, who underwent obstetric and gynecologic surgery previously, diagnosed with adenomyosis and UL more than the others who did not, but this seems to be a correlation rather than a causative association.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Date: 14.01.2015, Decision No: 02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Boosz AS, Reimer P, Matzko M, Römer T, Müller A. The conservative and interventional treatment of fibroids. Dtsch Arztebl Int 2014; 111: 877-83.
2. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect 2003; 111: 1037-54.
3. Islam MS, Protic O, Stortoni P, et al. Complex networks of multiple factors in the pathogenesis of uterine leiomyoma. Fertil Steril 2013; 100: 178-93.
4. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990; 94: 435-8.
5. Weiss G, Maseelall P, Schott LL, Brockwell SE, Schocken M, Johnston JM. Adenomyosis a variant, not a disease? Evidence from hysterectomized menopausal women in the Study of Women's Health Across the Nation (SWAN). Fertility and sterility 2009; 91: 201-6.
6. Shaikh H, Khan K. Adenomyosis in Pakistani women: four year experience at the Aga Khan University Medical Centre, Karachi. Journal of clinical pathology 1990; 43: 817-9.
7. García-Solares J, Donnez J, Donnez O, Dolmans M-M. Pathogenesis of uterine adenomyosis: invagination or metaplasia? Fertility and sterility 2018; 109: 371-9.
8. Chapron C, Vannuccini S, Santulli P, et al. Diagnosing adenomyosis: an integrated clinical and imaging approach. Human reproduction update 2020; 26: 392-411.
9. Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Semin Reprod Med 2010; 28: 204-17.
10. Evans P, Brunsell S. Uterine fibroid tumors: diagnosis and treatment. Am Fam Physician 2007; 75: 1503-8.
11. Payson M, Leppert P, Segars J. Epidemiology of myomas. Obstet Gynecol Clin North Am 2006; 33: 1-11.
12. Becker ER, Spalding J, DuChane J, Horowitz IR. Inpatient surgical treatment patterns for patients with uterine fibroids in the United States, 1998-2002. J Natl Med Assoc 2005; 97: 1336-42.
13. Becker ER. National trends and determinants of hospitalization costs and lengths-of-stay for uterine fibroids procedures. J Health Care Finance 2007; 33: 1-16.
14. Walker CL, Stewart EA. Uterine fibroids: the elephant in the room. Science 2005; 308: 1589-92.
15. Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2008; 22: 571-88.
16. Townsend DE, Sparkes RS, Baluda MC, McClelland G. Unicellular histogenesis of uterine leiomyomas as determined by electrophoresis by glucose-6-phosphate dehydrogenase. Am J Obstet Gynecol 1970; 107: 1168-73.
17. Benassayag C, Leroy MJ, Rigourd V, et al. Estrogen receptors (ERalpha/ERbeta) in normal and pathological growth of the human myometrium: pregnancy and leiomyoma. Am J Physiol 1999; 276: E1112-8.
18. Vannuccini S, Petraglia F. Recent advances in understanding and managing adenomyosis. F1000Research 2019; 8: 283.
19. Bergholt T, Eriksen L, Berendt N, Jacobsen M, Hertz JB. Prevalence and risk factors of adenomyosis at hysterectomy. Hum Reprod 2001; 16: 2418-21.
20. Panganamamula UR, Harmanli OH, Isik-Akbay EF, Grotegut CA, Dandolu V, Gaughan JP. Is prior uterine surgery a risk factor for adenomyosis? Obstet Gynecol 2004; 104: 1034-8.
21. Levgur M, Abadi MA, Tucker A. Adenomyosis: symptoms, histology, and pregnancy terminations. Obstet Gynecol 2000; 95: 688-91.
22. Polena V, Mergui J-L, Perrot N, Poncelet C, Barranger E, Uzan S. Long-term results of hysteroscopic myomectomy in 235 patients. European J Obstet Gynecol Reprod Biol 2007; 130: 232-7.
23. Medikare V, Kandukuri LR, Ananthapur V, Deenadayal M, Nallari P. The genetic bases of uterine fibroids; a review. J Reprod Inferti 2011; 12: 181.
24. Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril 2007; 87: 725-36.
25. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990; 94: 435-8.
26. Fields K, Neinstein L. Uterine myomas in adolescents: case reports and a review of the literature. J Pediatr Adolesc Gynecol 1996; 9: 195-8.
27. Fauconnier A, Chapron C, Babaki-Fard K, Dubuisson JB. Recurrence of leiomyomata after myomectomy. Human Reprod Update 2000; 6: 595-602.
28. Dreyfuss ML. Pathologic and clinical aspects of adenomyosis and endometriosis: A survey of 224 cases. Am J Obstet Gynecol 1940; 39: 95-9.
29. Curtis KM, Hillis SD, Marchbanks PA, Peterson HB. Disruption of the endometrial-myometrial border during pregnancy as a risk factor for adenomyosis. Am J Obstet Gynecol 2002; 187: 543-4.

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Smartphone-based videoconference visits are easy to implement, effective, and feasible in Crohn's disease patients: a prospective cohort study

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ABSTRACT

Aim: Crohn's disease patients require life-long follow-up resulting in frequent hospital visits. The benefits of telehealth have been established in the remote management of Crohn's disease but the role of mobile technology is missing. Our goal was to determine the feasibility and effectiveness of smartphone-based real-time video visits.

Material and Method: We followed 139 patients with either traditional (FTF) or online clinics (OLV) at a university hospital between May 2020- December 2020. We measured patients' satisfaction, disease activity, visit outcomes, socioeconomic parameters, and travel expenses to assess the effectiveness and acceptance of OLV.

Results: Satisfaction scores were significantly higher at OLV compared to FTF (89.58±9.93 vs 70.85±18.51, p<0.001). The Cronbach Alpha reliability coefficient of the VSQ9 scale was 0.878. A median of 47 km travel distance with a median travel time of 49 minutes per visit were saved with OLV. In terms of travel costs there was a potential saving of an average of US$12.24 per appointment. Eighty-five percent of the patients were successfully managed with online visits and did not require face-to-face visit.

Conclusion: There was a high level of acceptance for Smartphone-based real-time video visits in the distant management of Crohn's disease. The telehealth model was easy to implement, effective, with significant savings in travel costs and time.

Keywords: Crohn's disease, telehealth, COVID-19, cost of care

INTRODUCTION

Crohn's disease is an incurable chronic disease characterised by abdominal pain, diarrhea, fatigue and extra-intestinal manifestations. Patients often experience flares and remissions and require treatment across their lifespan. The burden of IBD (Inflammatory Bowel Disease) is rising in the Western World (1) with approximately 1 million individuals in the USA and 3.0-3.5 million in Europe.

Despite effective treatment options, a significant proportion of patients have suboptimal short and long-term outcomes. The obstacles for effective treatment include insufficient monitoring of symptoms, difficulty in getting timely access to a gastroenterologist, (2) and lead time, defined as the time interval between Crohn's disease-specific symptom onset and the establishment of a final diagnosis, to effective treatment (3).

Traditionally, healthcare providers (HCP) monitor and manage their patients face to face at in an office or outpatient setting. Travel time to the hospital, long waiting lists for outpatient appointments, difficulty in making an urgent appointment during disease flares, and need for prescriptions are possible barriers to getting quality care. Furthermore, the SARS COV-2 pandemic raised concerns among IBD patients, especially those on immunosuppressants or biologic agents, with possibly causing treatment delays (4).

Telehealth refers to remotely delivered healthcare between doctors and patients via telecommunication technologies, either with audio or video calls. Close monitoring of a patient's symptoms and adherence to medications can foster more rapid initiation or change in treatment, improve disease outcomes and QoL compared to standard medical care (5). Previously, a telehealth

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system consisting of a computer, a web-based clinician portal and a support server was found to be practical, acceptable to patients and led to improvements in patient satisfaction(6). A remote consultation program for underserved areas via a secure online platform reduced the time patients needed to wait to consult gastroenterologists (7).However, knowledge on the use of teleconference visits with smartphone as a telehealth tool is lacking.

The aim of the study was to evaluate the feasibility, acceptability, patient satisfaction and economic benefits of smartphone video-based telehealth in the management of Crohn's disease patients.

MATERIAL AND METHOD

Overview and Settings

The study was a prospective cohort study conducted at Kocaeli University's Faculty of Medicine. Once the COVID-19 virus breakthrough was declared a pandemic, the Turkish national security institution announced that virtual visits would be reimbursed to prevent viral contamination. Therefore, we initiated a smartphone-based real-time video visit in patients with Crohn's disease parallel to traditional visits between May and December 2020. Patients voluntarily chose to be included either in face-to-face (FTF) or online visits (OLV). We prospectively collected data to evaluate the effectiveness of online visits.

Inclusion and Exclusion Criteria

The study group included patients with documented Crohn's disease, based on clinical, endoscopic, and histologic findings who had been receiving treatment for more than six months. Participation in the study was offered to all consecutive patients over the age of 18. For patients without access to a smartphone, we provided one with an internet connection but patients were excluded from the study if they were unable to use smartphones due to visual challenges, deafness or mental disorders.

Description of the Study Groups and TELE-Health System

Patients were examined by two gastroenterologists (HY, AED) either at a video conference-based visit or FTF visit in the outpatient clinic. As a telehealth tool, we used the WhatsApp business application, which is freely available and encrypted end to end.

The online visit format was the same as that of a traditional FTF visit except for the physical examination. The national online medical information management system "e-nabız" was used to review laboratory, radiologic and pathology reports. Prescriptions were issued using the electronic prescription system "e-reçete," which allowed patients to receive their medications from the nearest pharmacy with the unique passwords provided at the OLV. (As compared to a traditional phone call visit, real-time video visits with smartphones enable the physician for a global assessment of the patient and allow patients to share their physical? Examination results instantly.) Face to face clinic patients were seen at the hospital outpatient clinics where standard of care was provided. Participants received a phone call from the administrative personnel the day after the visit, and a questionnaire about satisfaction and patient perceptions/preferences was applied. Participants received a phone call from the administrative personnel the day after the visit, with a questionnaire regarding satisfaction and patient perceptions/preferences. The patients informed that they would remain anonymous.

Outcome Measures

We used a validated, publicly available visit–specific satisfaction instrument (VSQ-9) to determine patient satisfaction. The VSQ-9 Questionnaire consisted of nine items to evaluate physician-patient relations, including the patient perception of the HCP's, technical skills and personal manner, the amount of time spent on the visits, waiting time for obtaining an appointment, waiting time at the office, accessibility of the office location, and quality of telephone service (8).

Disease activity was evaluated with the Harvey Bradshaw Index (HBI), where scores below 4 meant quiescent disease, and over 5 indicated active disease (9).

The distance and travel time between patients' homes and the hospital was calculated using the Google Maps application, taking into account the means of transport. We assessed levels of education, household environment, video quality, communication preferences and duration of visits, all of which might influence the use of telehealth technology. Parameters such as current medication, smoking status and, visit outcomes that can affect the course of Crohn's disease were recorded.

Sample Size and Statistical Analysis

Power analysis was performed using Gpower 3.1 to confirm a sample size of 52 detecting 80% power and alpha with 0.05 for telehealth outcomes between OL and FTF visits. All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Numeric variables were presented depending on a normal distribution with either mean±standard deviation, or median (IQR). Categorical variables were summarised as counts (percentages). Responses to VSQ9 which consists of a five-level scale was transformed linearly as the original study suggested(i.e., poor=0%; fair=25%; good=50%; very good=75%; and excellent=100%) (8).

Comparisons of numerical variables between groups were carried out using independent samples t-test or the Mann Whitney U test. The association between two categorical variables was examined by the Chi-square test. All statistical analyses were carried out with 5% significance, and a two-sided p-value<0.05 was considered statistically significant. Cronbach alpha, Factor Analysis (FA), and Bartlett's test statistics were used to determine the construct validity of the VSQ9 scale.

Ethical considerations

This study was performed in keeping with the principles of the Declaration of Helsinki. All participants were informed and signed the informed consent. The protocol was reviewed and approved by the Kocaeli University Ethical Committee of Clinical Researchs (Date:12.5.2020 Decision No:2020/123).

RESULTS

Baseline Demographics

Between May 2020 and December 2020, 180 patients were enrolled in the study (**Figure 1**). However, 36 (40%) participants from the FTF group and 5 (5%) from the OLV group were lost to follow up after recruitment. The reason for high drop out in the face-to-face group was concern by the patient of coronavirus contamination and unwillingness to complete the study questionnaires. Of the 139 patients included in analyses, the mean age was 45.41±13.33 (range 20-79), 52.5% were women (n=73). There was no significant difference between the clinical characteristics and disease activity between the OLV and FTF groups. Patients in the FTF group had significantly more Crohn's disease complications (p<0.001). Baseline descriptive features of the study population are presented in **Table 1**.

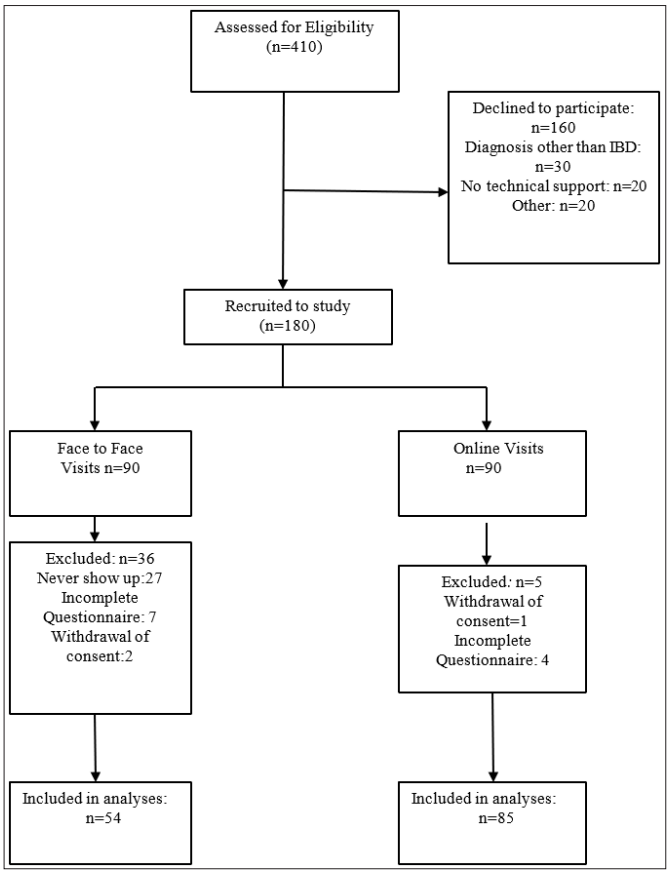

Figure 1. Flowchart of the study

Satisfaction Scores

The mean VSQ9 patient satisfaction score of the study population was 86,61±19.25. The mean VSQ9 satisfaction score was significantly higher in the OLV group (89.58±9.93) compared to FTF (70.85± 18.51) (p<0.001). Patients in the OLV group were more satisfied in terms of being able to contact the office by phone (OL vs. FTF, 90.77±19.04 vs 47.34±37.37; p<0.001), waiting time for the visit (84,62±19,61 vs. 51,06±25.51;p<0.001), getting an appointment (79,44±20,50 vs 58,51±;p<0.05), time spent with the HCP (91,15±16,78 vs 76,60±24,11; p<0.001), explanation of what was done at the visit (91,92±17,17 vs 80,32±23,27; p<0.05) , technical skills (93,85±12,52 vs 79,79±23,68 p<0.05) and the personal manner of the provider (93,08±14,99 vs 86,17±17,13; p<0.05) (**Figure 2**). The Cronbach's Alpha reliability coefficient of the VSQ9 scale was 0.878. Confirmatory Factor Analysis (CFA) was calculated as $\chi 2$=33,294 (sd=26; p=0.154) and RMSEA=0.051. It was determined that the scale had a high degree of internal consistency as it was valid as well as reliable.

Table 1. Baseline demographics of the study population (n=139)

	OLV (n=85)	FTF (n=54)	P Value
Age[a]	46.37±13.60	43.89±12.87	0.290
Gender, female	45 (52.9%)	28 (51.9%)	1.000
Active disease	27 (31.8%)	23 (42.6%)	0.264
Education Level			
Low	41 (48.2%)	26 (48.1%)	0.862
High	44 (51.8%)	28 (51.9%)	
Household Income			
Low	36 (42.3%)	18 (33.3%)	0.343
Middle	34 (40%)	29 (53.7%)	
High	15 (17.7%)	7 (13%)	
Smoking Status			
Non smoker	36 (42.4%)	15 (27.8%)	0.196
Smoker	29 (34.1%)	21(38.9%)	
Quitter	20 (23.5%)	18 (33.3%)	
Current Medication			
Amino salicylate	42 (49.4%)	24 (44.4%)	0.116
Steroid	34 (40%)	28 (51.8%)	0.164
Azathioprine	48 (56.4%)	36 (66.6%)	0.391
Anti -TNF	17 (20%)	18 (33.3%)	0.067
Complications	7 (8.2%)	19 (35.2%)	0.001
Disease Duration[a]	7.40± 5.91	5.43±4.98	0.038

Anti-TNF: Anti tumor necrosis factor, a: Mean (±SD)

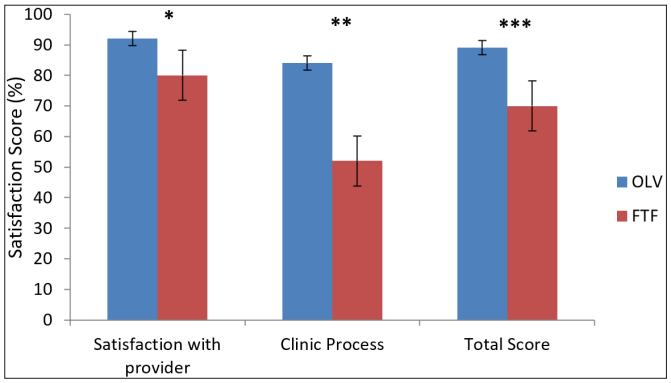

Figure 2. Mean VSQ-9 Satisfaction Scores
OLV: Online visits FTF: Face-to-face visits * p=0.001, ** p< 0.001, *** p< 0.001

Factors related to the Use of Technology

Participants were asked about their communication activities when using these communication devices. Text messaging 78 (91%) and video conference calls with friends and relatives 74 (87%) were the most common activities. Thirty-two per cent of the patients reported that they could not undertake video conference visits with their personal computers because of either non-availability of a PC (personal computer) or no confidence to operate. Smartphone ownership rates were not different between OLV patients and FTF patients (82% vs 86% p=0.253).

Patients rated voice and audio quality as good 72 (85.7%), fair 7 (8.3%), and bad 3 (3.6%). Video conference failed in 2 (2.4%) patients due to poor video and audio quality, where it was impossible to communicate, so it was converted to phone visits.

Visit Outcomes

Online visit outcomes were not significantly different from traditional visits. The median visit duration was 12 minutes (Median IQR: 10-14) in the OLV group and 15 (Median IQR:10-20) minutes in the FTF group. (p<0.05). The outcomes of the visits are summarised in **Table 2**. Thirteen patients (15.3%) in the OLV group were asked to come for physical examination due to the following symptoms severe abdominal pain 10 (11.8%), perianal disease 2 (2.4%), and uveitis 1 (1.1%). Sixty-one (71.7%) patients required required counselling regarding the impact of the Covid19 pandemic on Crohn's Disease during visits. Several OLV group patients asked whether if they still needed to come to a traditional outpatient clinic after online visits. Seventy-two (85.7%) participants reported no perceived need.

Economic Benefits of the Online Clinic

OLV and FTF participants reported that during the last year, they had presented to the hospital for Crohn's disease a median of four times (OLV vs FTF, 4 (IQR: 2-5 vs 4 (2.25-6); p=0.205). In our study population, 10 (7.5%) patients had even changed their residence to be closer to a hospital because of frequent visits. Neither median travel distance to the hospital from patients postal addresses (47 km (IQR: 24-108.5) vs 53 km (IQR (28.5-116.0) , p=0.686) nor the travel time (49 minutes (IQR: 33.50-98.50) vs ,59 minutes (IQR:36.50 -99.5) p=0.818) was different between OLV and FTF groups. Altogether, the online visits undertaken in the course of the study saved a total travel distance of 10,404 km and 8266-minute travel time compared to traditional visits. An average travel expense per visit of US$12.24 was saved, which is roughly 3% of the 2021 monthly minimum wage (US$385.80) in Turkey.

Table 2. Outcomes of the visits

	OLV (n=85)	FTF (n=54)	P value
Medication Dose Arrangement	11 (12.9%)	5 (11.1%)	ns
Medication Alteration	5 (5.9%)	3 (5.6%)	
Prescription for Refills	23 (27.1%)	12 (22.2%)	ns
Smoking Education	29 (31.7%)	20 (37.1%)	ns
Laboratory Tests	10 (24.7%)	14 (25.9%)	ns
Colonoscopy	4 (4.7%)	3 (5.5%)	ns
Hospitalisation	1 (1.2%)	2 (3.7%)	na

ns: non specific na:not applicable

DISCUSSION

In the present study, we demonstrated that smartphone-based real-time video visits offered a high-level of satisfaction and acceptance, were easy to implement and decreased travel cost and time.

Given the duration of Crohn's disease among the study's participants, their disease activity, percentage of Crohn's disease complications, socioeconomic spectrum and levels of education, our study population can be regarded as quite representative, and satisfaction results can be generalised.

Patient satisfaction with video visits was significantly higher than that of FTF visits. Furthermore, satisfaction scores with the provider and clinical process were found to be greater with online visits. Previously, Krier et al. (10) also reported high patient satisfaction and acceptance of videoconference telemedicine, but they found no difference in terms of satisfaction with a PC based telehealth system compared to regular outpatient clinics. Our results differed from the previous trial, possibly because of the use of a more flexible and commonly available technology. We believe that OLV were more user-friendly because of the ease of access to a physician possibility of obtaining a prescription by their phone instead of travelling to a hospital. Despite any special clinic time settings, the OLV group had a high satisfaction score with getting an appointment. Mobile technology may give patients more flexibility to connect to a hospital anywhere securing an

appointment. This form of making appointments may be more satisfying for patients. In fact, eHealth technologies such as web or text messages are mostly artificial. Online real-time communication with a health care professional is more realistic and hence increase acceptance.

Cooperation with technology is one of the most prominent hurdles of implementing telehealth. It is critically important to choose the right technological instrument when designing a telehealth model. Ninety-eight per cent of adults in Turkey use a mobile phone, while 77% use smartphones. Among smart telephone users, WhatsApp is currently available on 87.1% of them (11). Con et al. (12) evaluated IBD patients' eHealth perspectives and revealed that patients under 30 years old reported higher levels of confidence in using information and communication technologies. There was an inverse correlation between age and the use of smartphone apps. Additionally, computer anxiety was found to have a strong negative effect on the acceptance of telehealth services among seniors aged 50 or more (13). The mean age of our study population was slightly over 40 with the oldest patient was 69 years old. However, we were able to perform online visits successfully with both young and old patients. Entering data with a computer or smartphone app could be challenging, especially for older patients, but real-time video communication to physicians was effortless. The potential loss of privacy with a PC during work time might be another difficulty for the working age population. On the contrary, mobile technology is usable anytime and anywhere.

The online clinic led model of care was also found to be beneficial for socioeconomically disadvantaged patients. Patients with both lower levels of education and low incomes successfully completed the online visits. In contrast to Cross et al. (14) recent remote management model for IBD patients, which required a technical support line for participants and providers. participants in our study required neither theoretical and practical education nor technical support to conduct their visits. Real-time videoconferencing using a smartphone was found to be both feasible and easy to implement.

Online clinics saved an average of 47 km travelling distance and a median of 49 minutes travelling time per visit. When we add the waiting time at the office, and the interview itself, patients in the OLV group saved at least half a day. Our results were consistent with the findings of Ruf et al. (15). They also reported that the video conference clinic model reduced the travel distance (mean 310 km) and time per visit (314 minutes) in a rural setting and saved US$36 per visit. However, we do not believe telehealth is only efficient for rural populations. Our telehealth model also showed economic and logistic benefits for patients living in crowded metropolitans. Some patients reported that they moved their home closer to the hospital because of frequent hospital visits, which indicates that travelling is a burden. Costs related to the caregiver, food and parking costs, as well as indirect costs like missed work, should also be taken into account. According to one meta-analysis, one-third of the telehealth services using real-time video communication increased costs for the service provider (16). Telehealth technology consisting of a webpage and provider PC requires elements installed in the patients home. It has considerable costs for designing and operating a webpage. However, since we were able to take advantage of existing resources, there were no set-up expenses for our video visit model, such as website design, video conference software and hardware, technical equipment or physical space.

In our study, 15.3% of the patients had to come to FTF for physical examination or infusion therapy. İn such cases, OLV could not be considered an alternative to traditional visits. The combination of FTF and OLV may be the best practice and can reduce the burden on outpatient clinics.

Our study has some limitations. It was conducted under the extraordinary circumstances of the COVID-19 pandemic. Since the online clinic model can prevent virus dissemination, patients might express greater satisfaction, resulting in selection bias. Once the pandemic is over, patients' satisfaction perspectives may change. A hybrid visit model which combines online and traditional visits could be a solution for the demands of patients after COVID-19. One of our study's weaknesses was the absence of follow-up, but its primary aim was to evaluate acceptance, feasibility, and economic benefits. Future studies are needed to determine the long-term effects of OLV on disease activity QoL and medication adherence.

CONCLUSION

A smartphone-based video conference telehealth model does not require home installation or additional costs for implementation; it is accessible anywhere and is easy to use. This clinic model yielded widespread acceptance and good satisfaction rates. OLV also brought economic benefits to the patients. However, the long-term effects on disease activity and course need to be determined. We hope that this study will inspire others to implement telehealth to overcome barriers and deliver quality health care for patients with Crohn's disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The protocol was reviewed and approved by the Kocaeli University Ethical Committee of Clinical Researchs (Date: 12.5.2020 Decision No: 2020/123)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Burisch J, Jess T, Martinato M, Lakatos PL. The burden of inflammatory bowel disease in Europe. J Crohn's Colitis 2013; 7: 322–37.
2. Borren NZ, Conway G, Tan W, et al. Distance to specialist care and disease outcomes in inflammatory bowel disease. Inflamm Bowel Dis 2017; 23: 1234–9.
3. Danese S, Fiorino G, Peyrin-Biroulet L. Early intervention in Crohn's disease: Towards disease modification trials. Gut 2017; 66: 2179–87.
4. Mosli M, Alourfi M, Alamoudi A, et al. A cross-sectional survey on the psychological impact of the COVID-19 pandemic on inflammatory bowel disease patients in Saudi Arabia. Saudi J Gastroenterol 2020; 26: 263.
5. Elkjaer M, Shuhaibar M, Burisch J, et al. E-health empowers patients with ulcerative colitis: a randomised controlled trial of the web-guided 'Constant-care' approach. Gut 2010; 59: 1652-61.
6. Cross RK, Finkelstein J. Feasibility and acceptance of a home telemanagement system in patients with inflammatory bowel disease: a 6-month pilot study. Dig Dis Sci 2007; 52: 357–64.
7. Habashi P, Bouchard S, Nguyen GC. Transforming access to specialist sare for inflammatory bowel disease: The PACE telemedicine program. J Can Assoc Gastroenterol 2019; 2: 186–94.
8. Kennedy DM, Robarts S, Woodhouse L. Patients are satisfied with advanced practice physiotherapists in a role traditionally performed by orthopaedic surgeons. Physiother Can 2010; 62: 298–305.
9. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980; 315: 514.
10. Krier M, Kaltenbach T, McQuaid K, Soetikno R. Potential use of telemedicine to provide outpatient care for inflammatory bowel disease. Am J Gastroenterol 2011; 106: 2063–7.
11. Webrazzi Summit 2019 n.d.: 634. https://webrazzi.com /2019/10/24/turkiye-mobil-uygulama-kullanici-sayisi-gemius/ Gozde U. (accessed January 22, 2021).
12. Con D, Jackson B, Gray K, De Cruz P. eHealth for inflammatory bowel disease self-management - the patient perspective. Scand J Gastroenterol 2017; 52: 973–80.
13. Cimperman M, Makovec Brenčič M, Trkman P. Analyzing older users' home telehealth services acceptance behavior—applying an Extended UTAUT model. Int J Med Inform 2016; 90: 22–31.
14. Cross RK, Langenberg P, Regueiro M. et al. A randomized controlled trial of TELEmedicine for patients with inflammatory bowel disease (TELE-IBD). Am J Gastroenterol 2019; 114: 472–82.
15. Ruf B, Jenkinson P, Armour D, Fraser M, Watson AJ. Videoconference clinics improve efficiency of inflammatory bowel disease care in a remote and rural setting. J Telemed Telecare 2020; 26: 545–51.
16. Wade VA, Karnon J, Elshaug AG, Hiller JE. A systematic review of economic analyses of telehealth services using real time video communication. BMC Health Serv Res 2010; 10: 233.

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Vitamin D levels and in-hospital mortality of COVID-19

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ABSTRACT

Introduction: Vitamin D deficiency may be linked to an increased susceptibility risk of COVID-19. However, the data on the link between vitamin D levels and COVID-19 related in-hospital mortality is debatable. This study investigated whether vitamin D levels are associated with intensive care unit (ICU) admission and COVID-19 related in-hospital mortality.

Material and Method: We conducted a retrospective study with hospitalized COVID-19 patients between March 2020 and March 2021. 25 OH Vitamin D (Vit-D) levels <12 ng/mL were accepted as Vit-D deficiency. The patients were evaluated in two groups as Vit-D deficient and Non-Vit-D deficient. Groups were matched 1:1 by propensity score matching (PSM) regarding age and gender.

Results: A total of 192 patients, 52.6% (101) of whom were female, with a median age of 71 (IQR:61-78), were included in the study. Before PSM analysis, the Vit-D deficient group patients were older, female predominant, have more mortality rates. After PSM, 122 cases (61 cases for each group) remained, and mortality between Vit-D groups was statistically similar (34% vs. 26%, p=0.32). In the univariate logistics regression analysis before PSM, Vit-D level was a significant for mortality (OR:0.972 CI:0.945-0.999, p=0.044); after PSM statistical significance was lost (OR:0.96 CI:0.934-1.005, p=0.087). ICU admission rates were similar between groups.

Conclusion: Although mortality was higher in the group with Vit-D deficiency in the first analysis, it lost its significance on mortality after adjusting groups for age and gender. There was no relationship between vitamin D deficiency and COVID-19 in-hospital mortality.

Keywords: Vitamin D, COVID-19, mortality, critical care, hospitalization

INTRODUCTION

The benefits of vitamin D on bone health are well known. However, many studies have been conducted on the extra-skeletal effects of vitamin D (1). Serum total 25-OH Vitamin D (Vit-D) is often used to determine an individual's vitamin D level. Vitamin D is a pluripotent hormone that regulates immunity. (2,3).

With its various roles, such as interfering with adaptive and cell-mediated immunity and increasing antioxidant-related gene expression, vitamin D has played an adjunct position in preventing and treating acute respiratory infections (4,5). It is thought to prevent the progression to Acute Respiratory Distress Syndrome (ARDS) in viral diseases due to suppression of cytokine storm (5,6).

Although there are data on susceptibility and decreasing the severity of viral infections, conflicting results have been obtained in studies evaluating the effect of Vit-D levels on COVID-19 outcomes (7–9). This study was conducted to assess the relationship between Vit-D level, intensive care unit (ICU) admission and COVID-19 related in-hospital mortality.

MATERIAL AND METHOD

The study was carried out with the permission of the Çanakkale Onsekiz Mart University Medical Faculty Ethics Committee (Date: 09.06.2021, Decision No: 06-05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 192 patients hospitalized in Çanakkale Onsekiz Mart University Hospital diagnosed with COVID-19 between March 2020-March 2021 and whose Vit-D levels were measured during hospitalization were retrospectively included in the study. The diagnosis of COVID-19 was made by PCR positivity and/or radiological findings. Patients under 18 years old and pregnant were excluded from the study.

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The patients' laboratory values and clinical results were obtained from the hospital records. Those with Vit-D levels <12 ng/mL (30 nmol/L) were accepted as Vit-D deficiency (10). The patients were evaluated in two groups: Vit-D deficient and Non-Vit-D deficient (Vit-D levels ≥12 ng/mL). Participants in the Vit-D deficient group were matched 1:1 by propensity score matching (PSM) method to individuals in the Vit-D levels ≥12 ng/mL group in terms of age and gender. Participants were eligible for matching if their propensity scores were on the same support with a caliper width of 0.2 (11).

Serum 25(OH) vitamin D level was measured using the electrochemiluminescence immunoassay method in Cobas e 600 autoanalyzer device (Roche Diagnostics, F. Hoffmann-La Roche Ltd Kaiseraugst, Switzerland).

The CKD-EPI equation was used to compute the estimated glomerular filtration rate (eGFR) (12). Acute renal failure (ARF) was diagnosed by KDIGO(Kidney Disease: Improving Global Outcomes) criteria(13). Chronic kidney disease (CKD) was defined as a decreased estimated glomerular filtration rate (eGFR: <60 mL/min/1.73 m²). An album corrected the calcium called corrected calcium.

Statistical Analysis

Continuous variables are presented as the median and interquartile range (IQR: the difference between the 25th and 75th percentiles). Numbers and percentages were used to express categorical variables. Mann Whitney U test was used to compare the difference between groups of continuous variables. To determine the significance of the difference between categorical variables, Pearson's chi-square was performed. The Odds ratios (OR) were calculated using a 95% confidence interval (95 % CI). Statistical analyzes were performed using SPSS Version 19 (IBM, Armonk, NY, USA). Statistical significance was defined as two-sided p values of less than 0.05.

RESULTS

A total of 192 patients, 52.6% (101) of whom were female, with a median age of 71 (IQR:61-78), were included in the study. The intensive care unit admission rate in the study group was 35.4% (68), and the in-hospital mortality rate was 27.6% (53). The median hospital stay of the patients was 11 days (IQR: 6-17), and the median Vit-D level was 13.4 ng/mL (IQR: 7.9-22.9).

Data analysis without PSM

Before PSM analysis, Vit-D deficient group consisted of 82 (43%), and the Non-Vit-D Deficient group consisted of 110 (57%) participants. The Vit-D deficient group patients were older, female predominant, have more mortality rates and longer hospitalization lengths than Non-Vit-D Deficient group. ICU admission rates were similar between groups (43% vs. 30%, p=0.069). Vit-D deficient group patients have higher CRP levels, lower lymphocyte count, higher neutrophil/ lymphocyte ratio, higher parathormone, lower GFR, lower albumin and total protein levels. Diabetes, chronic obstructive pulmonary disease, hypertension, coronary artery disease, hyperlipidemia and cerebrovascular diseases history were similar in both groups. However, a history of CKD (33% vs 16%, p= 0.029) and ARF (63% vs 43%, p= 0.029) were higher in the Vit-D deficient group. The characteristics of the Vit-D deficient group and the non-Vit-D deficient group are shown in **Table 1**.

Data analysis after PSM

After age and gender matching with the PSM method, 122 cases (61 cases for each group) remained. After PSM, the effect of the Vit-D group on mortality lost its statistical significance. ICU admission rates were similar between groups (43% vs. 31%, p=0.19). The Vit-D deficient group had a longer hospital stay and lower lymphocyte levels. CKD history was higher, and GFR values were lower in the Vit-D deficient group. However, the ARF ratio was similar in both groups. Other comorbidities were similarly distributed in both groups. The characteristics of the groups after PSM are shown in **Table 2**.

In-hospital Mortality Analysis According to Vit-D Level

When the groups' mortality was evaluated with the Kaplan-Meier analysis, no significant difference was observed (Before PSM Log Rank p=0.309; After PSM Log Rank p=0.529). In the univariate logistics regression analysis before PSM, Vit-D level was a significant factor in predicting mortality (Beta: -0.029, Odds Ratio: 0.972 CI: 0.945-0.999, p=0.044); after PSM statistical significance was lost (Beta: -0.032, Odds Ratio: 0.96 CI: 0.934-1.005, p=0.087). Mortality rates according to Vitamin D groups before and after PSM are given in **Figure 1**.

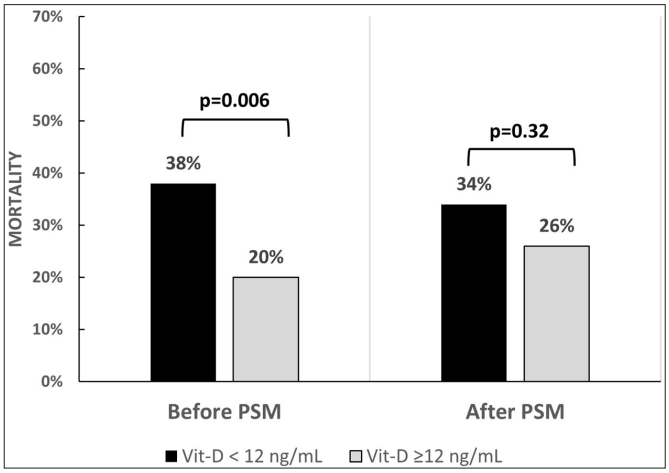

Figure 1. Mortality rates according to Vitamin D groups before and after PSM

Table 1. Comparison of groups with and without Vit-D deficiency before PSM

	Vit-D < 12 ng/mL n=82 (43%)	Vit-D ≥12 ng/mL n=110 (57%)	p
Female gender, n (%)	55 (67%)	46 (42%)	0.001
Age (years)	75 (67-81)	66 (59-76)	0.001
In-hospital mortality, n (%)	31 (38%)	22 (20%)	0.006
ICU Admission, n (%)	35 (43%)	33 (30%)	0.069
Length of hospitalization (days)	13 (8-18)	10 (6-16)	0.049
25 OH Vitamin D (ng/mL)	8 (5-10)	22 (15-31)	0.001
Serum glucose (mg/dl)	141 (104-166)	126 (103-165)	0.32
CRP (mg/dL)	5.1 (1.5-12.3)	1.7 (0.4-5.6)	0.002
Fibrinogen (mg/dl)	538 (427-647)	485 (393-784)	0.52
Procalcitonin (ng/ml)	0.35 (0.11-0.61)	0.11 (0.08-0.39)	0.23
White blood cell (10^3/Ul)	8.6 (5.8-12.2)	7.4 (5.8-9.9)	0.37
Lymphocyte (10^3/Ul)	0.70 (0.48-1.00)	1.03 (0.50-1.62)	0.004
Neutrophil (10^3/Ul)	7.4 (4.2-10.3)	6.1 (3.9-9.3)	0.30
Neutrophil/lymphocyte ratio	9 (5-17)	6 (3-14)	0.034
Parathormone (pg/ml)	224 (105-435)	118 (30-193)	0.032
eGFR (mL/dk/1.73m²)	32 (13-68)	75 (44-96)	0.001
Ionized calcium (mmol/l)	1.10 (1.04-1.17)	1.13 (1.06-1.21)	0.11
Albumin (g/dL)	2.86 (2.44-3.26)	3.38 (2.82-3.77)	0.001
Corrected calcium (mg/dL)	8.89 (8.49-9.36)	9.16 (8.62-9.43)	0.11
Phosphorus (mg/dl)	3.65 (2.96-5.23)	3.59 (3.00-4.24)	0.52
Total protein (g/dl)	5.61 (5.05-6.48)	6.10 (5.68-6.64)	0.014
Lactate dehydrogenase (U/l)	346 (253-463)	286 (224-379)	0.041
Uric acid (mg/dl)	5.70 (4.20-8.00)	5.20 (3.30-6.40)	0.024
Magnesium (mg/dL)	2.02 (1.63-2.32)	1.99 (1.79-2.18)	0.64

The numbers are given as the median (Interquartile Range). ICU: intensive care unit, eGFR: estimated glomerular filtration rate

Table 2. Comparison of groups with and without Vit-D deficiency after PSM

	Vit-D < 12 ng/mL N = 61 (50%)	Vit-D ≥12 ng/mL N = 61 (50%)	p
Female gender, n (%)	39 (64%)	39 (64%)	0.99
Age (years)	73 (64-79)	72 (65-78)	0.96
In-Hospital Mortality, n (%)	21 (34%)	16 (26%)	0.32
ICU Admission, n (%)	26 (43%)	19 (31%)	0.19
Length of hospitalization (days)	13 (8-19)	10 (5-15)	0.048
Serum Vitamin D (ng/mL)	7 (5-9)	23 (16-30)	<0.001
Serum glucose (mg/dl)	140 (110-165)	118 (104-163)	0.30
CRP (mg/dL)	5 (1-9)	3 (1-7)	0.19
Fibrinogen (mg/dl)	538 (431-612)	505 (422-763)	0.79
Procalcitonin (ng/ml)	0.18 (0.10-0.44)	0.16 (0.08-0.58)	0.98
White Blood Cell (10^3/uL)	8.5 (4.8-11.3)	7.2 (5.5-9.8)	0.70
Lymphocyte (10^3/uL)	0.70 (0.43-1.00)	1.00 (0.51-1.55)	0.015
Neutrophil (10^3/uL)	6.1 (4.8-9.7)	5.8 (3.5-9.1)	0.41
Neutrophil/lymphocyte ratio	9 (5-17)	5 (3-16)	0.087
Parathormone (pg/ml)	210 (79-428)	107 (48-181)	0.14
eGFR (mL/dk/1.73m²)	33 (14-71)	57 (31-89)	0.011
Ionized calcium (mmol/l)	1.11 (1.06-1.17)	1.10 (1.06-1.18)	0.90
Albumin (g/dL)	2.87 (2.52-3.29)	3.13 (2.54-3.71)	0.10
Corrected calcium (mg/dL)	8.83 (8.42-9.36)	9.00 (8.52-9.32)	0.50
Phosphorus (mg/dl)	3.64 (2.86-4.76)	3.51 (2.74-4.17)	0.50
Total protein (g/dl)	5.63 (5.06-6.60)	6.08 (5.68-6.55)	0.15
Lactate dehydrogenase (U/l)	325 (244-475)	287 (221-430)	0.29
Uric acid (mg/dl)	5.6 (4.1-7.9)	5.1 (3.2-6.7)	0.35
Magnesium (mg/dL)	1.98 (1.62-2.30)	1.82 (1.73-2.06)	0.37

The numbers are given as the median (Interquartile Range). ICU: intensive care unit, eGFR: estimated glomerular filtration rate

DISCUSSION

We found that mortality was higher in the Vit-D deficient group in the first evaluation before PSM. However, when the two groups were equalized by performing PSM in terms of age and gender, which are among the most significant markers of COVID-19 mortality, the mortality risk in the Vit-D deficient group lost its statistical significance. The true effect of Vit-D can be determined only after adjusting for crucial cofounders of mortality, such as age and gender. In this respect, PSM provides a more appropriate interpretation of the results (14).

The presence of vitamin D receptors (VDRs) and the activating enzyme 25-hydroxyvitamin D-1alpha-hydroxylase in immune cells partly explains vitamin D's immunological effects. Vitamin D, VDR and Retinoid X Receptor complex allow transcription of genes with antimicrobial activity such as cathelicidins and defensins (15). Because of the wide interindividual variation in gene expression in human cells in response to vitamin D treatment, some people may benefit more or less from it than others (3).

Low vitamin D levels may be linked to an increased susceptibility risk of COVID-19 (16,17). However, the data on the link between vitamin D levels and COVID-19 mortality is debatable. Although a meta-analysis with a high number of patients shows the association of low vitamin D with mortality(9), a more recent meta-analysis in which excluded biased studies could not show a relationship (7).

The lymphocyte count was also lower in the Vit-D deficient group after PSM. Low lymphocyte count may be due to impaired immune-modulatory effects caused by low vitamin D levels. Low lymphocyte levels have been detected frequently in COVID-19 (18,19). A correlation was found between lymphopenia and disease severity. ACE-2 receptors in lymphocytes are targets for COVID-19, which trigger programmed cell death processes in lymphocytes, and inhibit lymphocyte proliferation by increased inflammatory cytokines are possible causes of lymphopenia (20).

In the evaluation made after PSM, the hospitalization duration was longer in the Vit-D deficient group. In previous studies, no difference was found in the length of hospitalization (21,22). Using different cut-off levels for vitamin D deficiency in studies may explain this situation.

Although albumin levels were lower in the Vit-D Deficient group before PSM, there was no significant difference between them after PSM. It is known that albumin levels decrease as age increases (23). The Vit-D deficient group was older before PSM, and the difference after the equalization of age and gender with PSM may explain similar albumin levels. As an acute phase reactant, CRP levels were high in the Vit-D deficient group before PSM but lost their significance after PSM. Although some studies in the literature show that the acute phase reactants are higher in vitamin D deficiency (24), others do not support this data (25). In the studies, the groups were not balanced with PSM, and different criteria in the definition of vitamin D deficiency may explain this difference in acute phase reactants.

The kidneys may be the target of SARS-COV2; renal dysfunction may also significantly impact COVID-19 outcomes (26). Age and male gender are independent risk factors for renal dysfunction in COVID-19 patients (27). In our study, while ARF ratio was higher in Vit-D deficient group before PSM, it lost its significance among the groups after PSM. Chronic kidney disease was higher in the Vit-D deficient group before and after PSM. Vit-D deficiency is quite common in patients with CKD may explain this situation (28).

Calcium has essential roles in intracellular and metabolic signaling pathways, and it is critical for viral survival and virulence. (29). In a recent meta-analysis, patients with low calcium levels were shown to have higher COVID-19 disease severity and mortality (30). Although vitamin D deficiency is known as a cause of hypocalcemia, severe calcium deficiency is rarely reported (31). No difference was observed between the Vit-D groups regarding corrected calcium levels in our study.

Although our study is real-life data, its retrospective design and the fact that it was conducted during the pandemic are its main limitations. There are no other vitamin D-related measurements, such as the free fraction of 25-OH vitamin D, 1,25 dihydroxy vitamin D, and vitamin D binding protein. Some studies have analyzed patients' Vit-D levels prior to the diagnosis of COVID-19 (32,33). Although we used Vit-D levels during hospitalization to exclude this bias, the status of taking vitamin d supplements was not evaluated. Since our study is single-centered, it may not represent the general population.

CONCLUSION

Although mortality was higher in the group with vitamin D deficiency in the first analysis, it lost its significance on mortality after adjusting for age and gender. There was no relationship between vitamin D deficiency and COVID-19 in-hospital mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Çanakkale Onsekiz Mart University Medical Faculty Ethics Committee (Date: 09.06.2021, Decision No: 06-05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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REFERENCES

1. Bouillon R, Marcocci C, Carmeliet G, et al. Skeletal and extra-skeletal actions of vitamin D: current evidence and outstanding questions. Endocr Rev 2019; 40: 1109-51.
2. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-81.
3. Charoenngam N, Holick MF. Immunologic effects of vitamin D on human health and disease. Nutrients 2020; 12: 2097.
4. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients 2015; 7: 4240-70.
5. Mercola J, Grant WB, Wagner CL. Evidence regarding vitamin D and risk of COVID-19 and its severity. Nutrients 2020; 12: 3361.
6. Grant WB, Giovannucci E. The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918–1919 influenza pandemic in the United States. Dermatoendocrinol 2009; 1: 215-9.
7. Dissanayake HA, de Silva NL, Sumanatilleke M, et al. Prognostic and therapeutic role of vitamin D in COVID-19: systematic review and meta-analysis. J Clin Endocrinol Metab 2021; dgab892.
8. Ghasemian R, Shamshirian A, Heydari K, et al. The role of vitamin D in the age of COVID-19: A systematic review and meta-analysis. Int J Clin Pract 2021; 75: e14675.
9. Chiodini I, Gatti D, Soranna D, et al. Vitamin D status and SARS-CoV-2 infection and COVID-19 clinical outcomes. Front Public Health 2021; 9: 736665.
10. Giustina A, Adler RA, Binkley N, et al. Controversies in vitamin D: summary statement from an international conference. J Clin Endocrinol Metab 2019; 104: 234-40.
11. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10: 150-61.
12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604-12.
13. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120: c179-84.
14. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. multivar behav Res 2011; 46: 399-424.
15. Contreras-Bolívar V, García-Fontana B, García-Fontana C, Muñoz-Torres M. Vitamin D and COVID-19: where are we now? Postgrad Med 2021; 1-13
16. Liu N, Sun J, Wang X, Zhang T, Zhao M, Li H. Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. Int J Infect Dis 2021; 104: 58-64.
17. Düğeroğlu H. Evaluation of 25-hydroxy vitamin D levels in COVID-19 positive patients. J Health Sci Med 2021; 4: 931-5.
18. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020; 395: 497-506.
19. Yıldırım Ö, Bayram M, Özmen RS, et al. Evaluation of hematological indices in terms of COVID-19 related mortality and ICU admission. J Health Sci Med 2021; 4: 666-9.
20. Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. Immunol Lett 2020; 225: 31-2.
21. Pecina JL, Merry SP, Park JG, Thacher TD. Vitamin D status and severe COVID-19 disease outcomes in hospitalized patients. J Prim Care Community Health 2021; 12: 1-7
22. Reis BZ, Fernandes AL, Sales LP, et al. Influence of vitamin D status on hospital length of stay and prognosis in hospitalized patients with moderate to severe COVID-19: a multicenter prospective cohort study. Am J Clin Nutr 2021; 114: 598-604.
23. Weaving G, Batstone GF, Jones RG. Age and sex variation in serum albumin concentration: an observational study. Ann Clin Biochem 2016; 53: 106-11.
24. Oscanoa TJ, Amado J, Ghashut RA, Romero-Ortuno R. Relationship between serum 25-hydroxyvitamin D concentration and acute inflammatory markers in hospitalized patients with SARS-CoV-2 infection. Disaster Emerg Med J 2021; 6: 144-53.
25. Hernández JL, Nan D, Fernandez-Ayala M, et al. Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. J Clin Endocrinol Metab 2021; 106: e1343-53.
26. Bitencourt L, Pedrosa AL, de Brito SBCS, et al. COVID-19 and Renal Diseases: An Update. Curr Drug Targets 2021; 22: 52-67.
27. Xiang HX, Fei J, Xiang Y, et al. Renal dysfunction and prognosis of COVID-19 patients: a hospital-based retrospective cohort study. BMC Infect Dis 2021; 21: 158.
28. Franca Gois PH, Wolley M, Ranganathan D, Seguro AC. Vitamin D Deficiency in Chronic Kidney Disease: Recent Evidence and Controversies. Int J Environ Res Public Health 2018; 15: 1773.
29. Torres B, Alcubilla P, González-Cordón A, et al. Impact of low serum calcium at hospital admission on SARS-CoV-2 infection outcome. Int J Infect Dis 2021; 104: 164-8.
30. Alemzadeh E, Alemzadeh E, Ziaee M, Abedi A, Salehiniya H. The effect of low serum calcium level on the severity and mortality of Covid patients: A systematic review and meta-analysis. Immun Inflamm Dis 2021; 9: 1219-28.
31. Aldasouqi S, Glassy CM, Glassy MS, Treska A, Caldwell-McMillan M, Gossain V. Asymptomatic severe hypocalcemia secondary to vitamin d deficiency in an elderly patient. Case Rep Endocrinol 2011; 2011: e830952.
32. Ünsal YA, Gül ÖÖ, Cander S, et al. Retrospective analysis of vitamin D status on ınflammatory markers and course of the disease in patients with COVID-19 infection. J Endocrinol Invest 2021; 44: 2601-7.
33. Hastie CE, Pell JP, Sattar N. Vitamin D and COVID-19 infection and mortality in UK Biobank. Eur J Nutr 2021; 60: 545-8.

Original Article

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The effect of altitude difference on gastrointestinal bleeding in the chronic period

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ABSTRACT

Aim: The susceptibility to gastrointestinal bleeding is observed with an increase in altitude. There is no recommendation regarding altitude in terms of drug selection and dose to be used in diseases requiring antiaggregant and anticoagulant use. In this study, we aimed to determine whether there is a difference between gastrointestinal bleeding requiring hospitalization due to the use of antiaggregant and/or anticoagulant therapy between two populations living at different altitudes.

Material and Method: This retrospective study was performed in two secondary care hospitals. Patients from Group B living in villages with an altitude of 9842 ft and above and Group F patients living in an area with an altitude of 30 ft were included. Patient's demographic data, co-morbid diseases, antiaggregant and anticoagulant use, hemoglobin, hematocrit, MCV values and platelet count were noted.

Results: The study included a total of 118 patients with gastrointestinal bleeding. There was no statistically significant difference between the groups in terms of the drugs used by the patients, the types and numbers of drugs.

Conclusion: We found that there was no significant difference between the groups with different altitudes in terms of drugs used by patients with gastrointestinal bleeding, drug types and numbers.

Keywords: Gastrointestinal bleeding, high altitude, antiaggregant, anticoagulant.

INTRODUCTION

With increasing life expectancy, the prevalence of coronary artery disease, atrial fibrillation and cerebrovascular disease and accordingly the frequency of single or multiple antiaggregant and anticoagulant treatment has been increasing (1-3). While recommending antiaggregant or anticoagulant therapy for these diseases, the guidelines recommend that we choose drugs according to the patient's angiographic presence, weight, GFR, age, and other co-morbidities criteria (4,5). However, there are no recommendations in the guidelines regarding the altitude at which patients live.

In studies conducted on people who need to work at high altitudes such as workers, mountaineers and soldiers, it has been observed that acute mountain sickness (AMS), high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE) develop more frequently as altitude increases (6-9). It is known that gastrointestinal symptoms are common findings in AMS that occurs after hypoxia and hypobaric environment (10,11). It was observed that gastrointestinal symptoms and gastrointestinal bleeding (GIB) increased with increasing altitude (12,13).

As the altitude increases, the increase in hemoglobin value and the amount of platelet increases to adapt to the developing hypoxia due to elevation (14,15). Earlier studies have shown that polycythemia, which is seen as high altitude, is a risk of gastrointestinal bleeding (7,16,17).

In this study, we investigated whether there was a difference between gastrointestinal bleeding that lived at two different altitudes and requiring hospitalization and gastrointestinal bleeding due to antiaggregant and/or anticoagulant treatment.

MATERIAL AND METHOD

The study was carried out with the permission of Muğla Sıtkı Koçman University Health Sciences Ethics Committee (Date: 19.10.2020, Decision No: 15). The study was carried out in accordance with the principles of the Declaration of Helsinki and the ethical rules.

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Study Design and Settings

The study was planned as a retrospective. Group B is a center with 3050 ft. The patients included in this center were from the villages with an altitude of 9842 ft and above. Group F has at 30 ft altitude. Data of patients were examined from both state hospitals between 30 June 2015 and 30 June 2020.

Selection of the Participants

Patients aged 18 years and older who were hospitalized with the diagnosis of gastrointestinal bleeding were included in the study. Hematemesis, melena, hematochezia, and presence of the fecal occult blood were accepted as gastrointestinal bleeding symptoms.

The patients with known cancer, hepatic diseases, and whose INR above the therapeutic value (INR>3,5) were excluded from the study. The patients who have not enough data also have been excluded. In accordance with the power analysis, each group included 59 patients.

Measurements and Outcomes

The demographic data, chronic diseases, and the drugs were examined in each group.

Statistical Analysis

Descriptive statistics were given as mean±standard deviation and median with minimum-maximum values for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. The normal distribution of the numerical variables was analyzed by the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests.

In comparing two independent groups, the Independent Samples t-test was used where numerical variables had a normal distribution. For variables without normal distribution, the Mann-Whitney U test was applied. The Pearson Chi-Square and Fisher's Exact tests were used in 2x2 tables to compare categorical variables.

For statistical analysis, "Jamovi project (2020), Jamovi (Version 1.6.22.0) [Computer Software] and JASP (Version 0.14.1) were used. The significance level (p-value) was set at 0.05 in all statistical analyses.

RESULTS

In this study, each group included 59 patients. Demographic and clinical characteristics of the patients in Group B and Group F are summarized in Table 1. The mean age and sex distribution of the patients were similar in both groups (p>0.05). Group B and Group F had at least one co-existing disease (62.7% vs 69,5%)(p=0.437). Hypertension was the most common co-morbid disease seen in both groups. There were 35(59.3%) patients with hypertension in group B and 37(62.7%) patients in group F. Distribution of the co-existing diseases was similar between two groups except for coronary artery disease. There were significantly more patients with coronary heart disease in Group B than Group F (n=15, 40.7% vs. n=9, 25.4%, p=0.013) (**Table 1**).

Table 1. Demographic and clinical characteristics of the patients

	Group B (n=59)	Group F (n=59)	p
Age (year) †, ‡			0.855**
	66.1±17.9	66.1±19.1	
	70.0 [31.0-93.0]	72.0 [26.0-91.0]	
Sex §			0.999*
Female	26 (44.1)	27 (45.8)	
Male	33 (55.9)	32 (54.2)	
Coexisting diseases, yes §	37 (62.7)	41 (69.5)	0.437*
Coronary artery disease	24 (64.9)	15 (36.6)	0.013*
Heart failure	11 (29.7)	8 (19.5)	0.294*
Diabetes mellitus	14 (37.8)	17 (41.5)	0.744*
Hypertension	35 (94.6)	37 (90.2)	0.678*
Cerebrovascular accident	6 (16.2)	5 (12.2)	0.610*
Dysrhythmia	10 (27)	12 (29.3)	0.826*
Peripheral artery disease	2 (5.4)	0 (0)	0.222*
Medications, yes §	31 (52.5)	27 (45.8)	0.461*
Anti-aggregant drugs			
Acetylsalicylic acid	22 (71)	13 (48.1)	0.076*
Clopidogrel	10 (32.3)	9 (33.3)	0.931*
Ticagrelor	0 (0)	0 (0)	-
Prasugrel	0 (0)	0 (0)	-
Anti-coagulant drugs §			
Warfarin	5 (16.1)	7 (25.9)	0.358*
Rivaroxaban	3 (9.7)	2 (7.4)	0.999*
Dabigatran	0 (0)	1 (3.7)	0.466*
Apixaban	2 (6.5)	1 (3.7)	0.999*
Edoxaban	0 (0)	1 (3.7)	0.466*
Enoxaparin	1 (3.2)	0 (0)	0.999*
Number of drugs ‡	1.0 [1.0-3.0]	1.0 [1.0-2.0]	0.510**
Number of patients using §			0.646*
No medication	28 (47.5)	32 (54.2)	
One drug	21 (35.6)	20 (33.9)	
Two drugs	8 (13.6)	7 (11.9)	
Three drugs	2 (3.4)	0 (0)	

†: mean±standard deviation, ‡: median [min-max], §: n (%), *. Pearson Chi-Square, Fisher's Exact, or Fisher Freeman Halton tests. **. Mann-Whitney U test, ***. Independent Samples T-Test

The groups had similar rates in terms of the drugs used by the patients, types and numbers of drugs (p>0.05) (**Table 1**). Acetylsalicylic acid and clopidogrel were the most frequently used antiaggregant drugs in both groups (**Table 1**). As anticoagulant, warfarin and rivaroxaban were common drugs in both groups.

Table 2 presents the laboratory findings. Although the mean hemoglobin value was lower in Group F than Group B, the difference between the groups was not statistically significant (p=0.085). The median platelet count was significantly lower in Group B than Group F (205.0 vs. 263.0, p=0.002).

Table 2. Laboratory findings of the patients.

	Group B (n=59)	Group F (n=59)	p
Laboratory findings			
Hemoglobin (g/dL) †	10.3±2.9	9.4±2.6	0.085***
Hematocrit (%) †	31.4±8.6	29.2±7.5	0.136***
MCV (fL) ‡	87.0 [59.0-102.0]	88.3 [66.0-103.8]	0.617**
Platelet count (103/µL) ‡	205.0 [80.0-664.0]	263.0 [48.0-496.0]	0.002**

†: mean±standard deviation, ‡: median [min-max], §: n (%), MCV: mean corpuscular volume.

DISCUSSION

In our study, we examined the epidemiology of patients with gastrointestinal bleeding at different altitudes; we did not find a significant difference between altitude and the number of drugs that cause bleeding, and the type of drug. The most common chronic disease was hypertension in both groups. A statistical difference was observed in high altitude in terms of coronary artery disease distribution in patients. Hemoglobin values were lower in the low altitude region, but there was no statistically significant difference. Platelet count was lower in the high-altitude region.

In both groups, GI bleeding was observed in almost half of the patients, despite the fact that no medication was used. We hypothesize that this is due to the relatively advanced age of the patient population in the study. Because we know that the incidence of GIB increases with age and patients particularly over 60 year of age are prone to bleeding (18,19).

According to the studies on high altitude related gastrointestinal bleeding, there prevelance of bleeding were more common in males (7,20). However, in our study, no difference was found between males and females in terms of bleeding in both groups. This may be due to the relatively small number of the population in the study or that the studies on high altitude are related to workers dominated by male workers.

It is known that an increase in the number of erythrocytes occurs as a result of erythropoietin release and polycythemia occurs to increase the oxygen-carrying capacity of the blood in terms of adaptation to hypoxia at high altitudes (9,21). There are many studies showing that the hemoglobin value increases after stimulation of erythropiesis, which occurs as a result of erythropoietin release in people at high altitudes (6,8,14,22-24). In our study, the hemoglobin value of the patients was higher in the high altitude region; but no statistically significant difference. The reason may be that the patients included in the study were patients who had blood loss due to active gastrointestinal bleeding.

The frequency of gastrointestinal bleeding is higher, especially in the first 3 weeks, in those who travel temporarily to these areas rather than living in high-altitude areas (25,26). The main reason why there was no difference in the rates of GI bleeding due to altitude difference in the patients in this study is that they live in those regions constantly.

Peptic ulcer disease, alcohol consumption and non-steroidal antiinflamatory drug use are main predisposing factors for gastrointestinal bleeding (12,27,28). Additionally, the use of antiaggregant and anticoagulant increases the frequency of GIB (29,30). In our study, it was observed that the most frequently used antiaggregants were acetylsalicylic acid and clopidogrel among the drug users, but there was no statistical difference. The reason why the use of prasugrel and ticagrelor as antiaggregants was not detected in patients with GIB may be the administration of clopidogrel together with fibrinolytic therapy to acute myocardial infarctions, and afterwards continue, since there was no angiography unit in both center.

There are several reasons why there is no difference in gastrointestinal bleeding between people living at both altitudes. First, hematological changes required for gastrointestinal bleeding to occur generally begin after 3500 meters. In an investigation, Wu et al. (7) showed that GIB rarely found below 3500 meters. In our study, patients living at an altitude of 9842 ft (3000 meters) and above were taken as the high altitude group. Second, the rate of coronary artery disease is high in the population living at high altitudes, and proton pump inhibitors, which are frequently used while using antiaggregants, may have affected the bleeding rate in that group. Third, since the awareness of drug use is relatively weak in populations living in rural areas, and due to the irregular use of drugs, bleeding rates may have been relatively lower.

The limitation of this study is relatively small size of patient population. Another limitation is patients with high risk potential for bleeding (cancer, hepatic disease, high INR) were not included in the study due to the exclusions criters that would increase bleeding susceptibility.

CONCLUSION

Altitude has an effect on the frequency and risk of GI bleeding. However, this effect is closely related to the degree of altitude, whether there is an acute exposure to altitude difference, the drugs used and age. Since these criteria were not completely present in our study, no significant difference was found. Larger studies are needed to obtain more accurate information on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Muğla Sıtkı Koçman University Health Sciences Ethics Committee (Date: 19.10.2020, Decision No: 15).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021; 42: 373-498.
2. Caprio FZ, Sorond FA. Cerebrovascular disease: primary and secondary stroke prevention. Med Clin North Am 2019; 103: 295-308.
3. Gremmel T, Michelson AD, Frelinger III AL, Bhatt DL. Novel aspects of antiplatelet therapy in cardiovascular disease. Res Pract Thromb Haemost 2018; 2 : 439-49.
4. Buckley LF, Rybak E, Aldemerdash A, Cheng JW, Fanikos J. Direct oral anticoagulants in patients with atrial fibrillation and renal impairment, extremes in weight, or advanced age. Clin Cardiol 2017; 40: 46-52.
5. Villain C, Liabeuf S, Metzger M, et al. Impact of age on cardiovascular drug use in patients with chronic kidney disease. Clin Kidney J 2020; 13: 199-207.
6. Fruehauf H, Vavricka SR, Lutz TA, et al. Evaluation of acute mountain sickness by unsedated transnasal esophagogastroduodenoscopy at high altitude. Clin Gastroenterol Hepatol 2020; 18: 2218-25.
7. Wu TY, Ding SQ, Liu JL, et al. High-altitude gastrointestinal bleeding: an observation in Qinghai-Tibetan railroad construction workers on Mountain Tanggula. World J Gastroenterol 2007; 13: 774-80.
8. Waeber B, Kayser B, Dumont L, Lysakowski C, Tramer MR, Elia N. Impact of study design on reported incidences of acute mountain sickness: a systematic review. High Alt Med Biol 2015; 16: 204-15.
9. Cerit M, Erdoğan M. Yüksek irtifa fizyolojisi ve adaptasyonun askeri fiziksel hazırlık seviyesine etkilerinin değerlendirilmesi. Kara Harp Okulu Bilim Dergisi 2019; 1: 1-15.
10. Wang SH, Chen YC, Kao WF, et al. Epidemiology of acute mountain sickness on Jade Mountain, Taiwan: an annual prospective observational study. High Alt Med Biol 2010; 11: 43-49.
11. Richalet JP, Julia C, Lhuissier FJ. Evaluation of the Lake Louise Score for acute mountain sickness and its 2018 Version in a cohort of 484 trekkers at high altitude 2021; 22: 353-61.
12. Wu TY, Ding SQ, Liu JL, et al. Who should not go high: chronic disease and work at altitude during construction of the Qinghai-Tibet railroad 2007; 8: 88-107.
13. Khanna K, Mishra KP, Ganju L, Kumar B, Singh SB. High-altitude-induced alterations in gut-immune axis: a review. Int Rev Immunol 2018; 37: 119-26.
14. Gassmann M, Mairbäurl H, Livshits L, et al. The increase in hemoglobin concentration with altitude varies among human populations. Ann N Y Acad Sci 2019; 1450: 204-20.
15. Hudson JG, Bowen AL, Navia P, et al. The effect of high altitude on platelet counts, thrombopoietin and erythropoietin levels in young Bolivian airmen visiting the Andes. Int J Biometeorol 1999; 43: 85-90.
16. Li K, Gesang L, He C. Mechanism of apoptosis involved in gastric mucosal lesions in Tibetans with high-altitude polycythemia. Exp Ther Med 2017; 14: 3780- 3787.
17. Aksel G, Çorbacıoğlu ŞK, Özen C. High-altitude illness: Management approach. Turk J Emerg Med 2019; 19: 121-6.
18. Aktaş HŞ. The role and importance of antiagregan, anticoagulant drugs in the etiology of upper gastrointestinal system bleeding in elderly. Haydarpaşa Numune Med J 2019; 59: 250-255.
19. Lenti MV, Pasina L, Cococcia S, et al. Mortality and risk factors for gastrointestinal bleeding in elderly patients. Eur J Intern Med 2019; 61: 54-61.
20. Mahajan P, Chandail VS. Etiological and endoscopic profile of middle aged and elderly patients with upper gastrointestinal bleeding in a tertiary care hospital in North India: a retrospective analysis. J Midlife Health 2017; 8: 137-41.
21. Heikura IA, Burke LM, Bergland D, Uusitalo ALT, Mero AA, Stellingwerff. Impact of energy availability, health, and sex on hemoglobin-mass responses following live-high-train-high altitude training in elite female and male distance athletes. Int J Sports Physiol Perform 2018; 13: 1090-6.
22. Akunov A, Sydykov A, Toktash T, Doolotova A, Sarybaev A. Hemoglobin changes after long-term intermittent work at high altitude. Front Physiol 2018; 9: 1152.
23. Moore LG. Measuring high-altitude adaptation. J Appl Physiol 2017; 123: 1371-85.
24. Storz JF, Cheviron ZA. Physiological genomics of adaptation to high-altitude hypoxia. Annu Rev Anim Biosci 2021; 9: 149-71.
25. Mieske K, Flaherty G, O'Brein T. Journeys to high altitude-risks and recommendations for travelers with preexisting medical conditions. J Travel Med 2010; 17: 48-62.
26. Amatya B, Lakhey PJ, Pandey P. Perforation peritonitis at high altitude. JNMA J Nepal Med Assoc 2018; 56: 625-8.
27. Vearrier D, Greenberg MI. Occupational health of miners at altitude: adverse health effects, toxic exposures, pre-placement screening, acclimatization, and worker surveillance. Clin Toxicol (Phila) 2011; 49: 629-40.
28. Agarwal A, Benias P, Gutierrez OIB, et al. Endoscopic suturing for management of peptic ulcer-related upper gastrointestinal bleeding: a preliminary experience. Endosc Int Open 2018; 6: 1439-44.
29. Lv M, Zheng X, Wu T, et al. A new score for predicting acute gastrointestinal bleeding in patients administered oral antiplatelet drugs. Front Pharmacol 2021; 11: 2245.
30. Solakoğlu T, Köseoğlu H, Atalay R, et al. Impact of anti-aggregant, anti-coagulant and non-steroidal anti-inflammatory drugs on hospital outcomes in patients with peptic ulcer bleeding. Saudi J Gastroenterol 2014; 20: 113-9.

Original Article

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Evaluation of thyroid dysfunctions frequency in the first trimester

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ABSTRACT

Aim: The aim of the study is to determine the frequency of first-trimester thyroid dysfunction in pregnant women and to investigate the effect of thyroid dysfunction on some perinatal outcomes.

Material and Method: In the study, first-trimester Thyroid stimulating hormone (TSH), free T4 and free T3 hormone values of pregnant women who applied to our outpatient clinic were retrospectively scanned and recorded. As a result, 3224 pregnant women were included in the study. Pregnant women were evaluated as overt hypothyroidism, subclinical hypothyroidism, overt hyperthyroidism, subclinical hyperthyroidism and euthyroid according to TSH and fT4 values. Results of thyroid function tests of pregnant women and some perinatal results (age, gestational week, delivery type, baby gender, birth weight, gravida, parity, abortion) were compared

Results: In our study, the mean age of the pregnant women for screening was 28.6±3.1, the mean birth week was 38.7±2.1, and the mean birth weight was 3037±324.73.6% (n=2369) of the pregnant women were normal euthyroid, 0.71% (n=23) were subclinical hyperthyroidism, 0.65% (n=23) were overt hyperthyroidism, while 15.6% (n=507) were overtly hypothyroid and 9.4% 3 (n=304) were found to be subclinical hypothyroidism. A significant statistical difference was not found between thyroid outcome test results and perinatal outcomes (age, gravida, parity, abortion, birth strength, gestational age, delivery type, babies) (p> 0.05).

Conclusion: In our study, a high prevalence of thyroid disease, especially hypothyroidism, was observed in pregnant women. More studies should be done to evaluate the effect of thyroid functions on pregnancy outcomes.

Keywords: First trimester, pregnancy, thyroid dysfunction, TSH, perinatal outcomes

INTRODUCTION

Many significant changes occur in thyroid function and physiology during pregnancy. The second most common endocrinological disorder in women of reproductive age is thyroid diseases (1). Thyroid hormone has very important roles in fetal development, maturation, normal placentation, normal fetal brain development, neuronal proliferation, migration, structural organization and embryogenesis. These events occur especially in the first and second trimesters when the fetus meets the primary thyroid hormone requirement from the mother. 8-10. in weeks of pregnancy fetal thyroid gland starts to concentrate iodine and to synthesize hormones after 12 weeks of gestation. Hormone production is limited until the twentieth gestational week (2). In the first trimester, the basal ganglia, cochlea and cerebral neo-cortex develop rapidly and become hypersensitive to iodine deficiency (3). After the maturation of the pituitary gland at the twentieth gestational week, iodine retention and hormone synthesis increase in the fetal thyroid follicular cell. Until the last period of pregnancy, total T4 and free T4 concentration increase regularly in the fetal circulation (4).

Concomitant low TSH with normal fT3 and fT4 values is associated with subclinical hyperthyroidism. High fT3 and fT4 values together with low TSH suggest overt hyperthyroidism. Glucocorticoid or dopamine use, euthyroid sick syndrome, hunger, weight loss, pregnancy, hypothalamic or pituitary deficiencies are other conditions that cause low TSH. In the case of high TSH, if low free T4 is present (obvious), hypothyroidism should be considered. While free T4 and free T3 are normal, elevated TSH is associated with subclinical hypothyroidism (5).

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Subclinical hypothyroidism is the most common thyroid dysfunction in pregnant women. Overt hypothyroidism is found in 0.3-0.5% of pregnant women, and subclinical hypothyroidism is found in 2-2.5% (6,7). The complications of maternal hypothyroidism related to the fetus are fetal distress, intrauterine growth retardation, premature birth, spontaneous abortion and stillbirth. Maternal complications are anaemia, preeclampsia, ablation placenta, postpartum haemorrhage, delayed lactation, and maternal delay (8). Overt hyperthyroidism is relatively rare and is seen in 0.2% of pregnancies. Subclinical hyperthyroidism is seen in 1.7% of pregnancies. The most common cause of thyrotoxicosis during pregnancy is Graves' disease (9).

In this study, we aimed to determine the frequency of first-trimester thyroid dysfunction in pregnant women who applied to our outpatient clinic and gave birth in our clinic and to evaluate the effect of thyroid dysfunction on some perinatal outcomes.

MATERIAL AND METHOD

The study was carried out with the permission of Van Ministry of Health University Training and Research Hospital Clinical Research and Ethics Committee (Date: 07/03/2019, Decision No: 2019/05). Verbal consent was obtained from the patients included in the study or, if necessary, from their legal representatives, and our study was conducted in accordance with the Principles of the Declaration of Helsinki.

In the study, the data of pregnant women who had thyroid function tests (TFT) at the time of admission in the first trimester at the Van Ministry of Health University Training and Research Hospital Gynecology and Obstetrics Clinic between 2015 and 2018 were retrospectively reviewed. A total of 3224 pregnant women, including 2369 pregnant women with normal thyroid function tests and 855 pregnant with pathology in thyroid function tests, were included in the study.

Thyroid dysfunction frequencies of the patients were evaluated so that the reference range of thyroid tests was 0.27-4.2U/L, 12-22 pmol/L, 3.1-6.8 pmol/L for TSH, fT4, fT3, respectively. The patients were diagnosed with euthyroidism, overt hyperthyroidism, overt hypothyroidism, subclinical hyperthyroidism, and subclinical hypothyroidism within these reference ranges. In the study, the perinatal results (gravida, age, gestational week, parity, gestational week, baby gender, birth weight and delivery type) and thyroid function test results were compared in patients who had first-trimester thyroid function tests in our hospital

The data were analyzed using the SPSS 20.0 package program. Student's t-test was used for comparing the means between independent groups, and the chi-square test was used to compare categorical variables. Descriptive statistical methods (number, mean, standard deviation) were used. P <0.05 was considered significant.

RESULTS

3224 pregnant women participated in our study. Of the pregnant women in the study, 73.6% (n=2369) had euthyroidism, 0.7% (n=23) subclinical hyperthyroidism, 0.6% (n=21) overt hyperthyroidism, 15.6% (n=507) overt hypothyroidism and% Subclinical hypothyroidism was detected in 9.4 (n=304) of them. In the study, there was no significant difference between the groups in terms of the week, age, the number of abortions, parity, and gravida (p> 0.05). The groups according to TFT week, age, abortion, gravida, and parity are shown in **Table 1**.

The mean birth week of the groups in our study was 38.7±2, and the mean birth weight was 3037±324 grams. There was no statistically significant difference between the groups in terms of the birth week and baby birth weight (p> 0.05). 64.5% (n=2078) of the pregnant women delivered normal delivery, 35.5% (n=1146) had cesarean delivery. Although hyperthyroidism and subclinical hypothyroidism were seen more after euthyroidism in normal and cesarean deliveries, no significant difference was observed between the groups according to the type of delivery (p> 0.05). In our study, it was determined that 1617 (50.2%) male babies and 1607 (49.7%) female babies were born. Although hyperthyroidism and subclinical hypothyroidism were seen more after euthyroidism in both genders, no significant difference was observed between the groups according to gender (p> 0.05). The evaluation of the groups according to the birth week, birth weight, birth type, and baby gender is shown in **Table 2**.

Table 1. Evaluation of groups according to TFT week, age, abortion, gravida, parity

	Euthyroidism n (%)	Hyperthyroidism n (%)	Hypothyroidism n (%)	Subclinical hyperthyroidism n (%)	Subclinical hypothyroidism n (%)	P
	2369 (73.6%)	21 (0.6%)	507 (15.6%)	23 (0.7%)	304 (9.4%)	
*TFT (week)	9.1±2.1	9.4±1.4	8.9±3.2	9.0±1.1	9.2±2.8	0.23
Age(year)	28±4.1	29±3.2	29±3.8	28±4.7	29±2.5	0.52
Abortion(n)	1.1±0.4	0.9±0.2	1.0±0.2	0.8±0.4	0.9±0.1	0.23
Parity(n)	2.1±0.4	1.8±0.6	2.1±0.4	1.9±0.2	2.0±0.1	0.34
Gravida(n)	3.0±1.5	2.1±1.0	2.9±0.4	2.5±1.1	3.3±1.4	0.65

*TFT: Thyroid function test

Table 2. Evaluation of the groups according to birth week, birth weight, mode of delivery and baby gender

	Euthyroidism n (%)	Hyperthyroidism n (%)	Hypothyroidism n (%)	Subclinical hyperthyroidism n (%)	Subclinical hypothyroidism n (%)	Total	P
Birth week	39.1±2.4	38.2±3.2	38.9±3.3	39.3±2.2	38.5±3.2	38.7±2.1	0.67
Birth weight (gr)	3118.2±457	3230.3±644.1	3061.5±512.7	3168.5±678.5	3038.4±687.4	3037.1±324.4	0.45
Cesarean (n)	823 (71.8%)	8 (0.7%)	192 (16.8%)	5 (0.4%)	118 (10.3%)	1.146 (100%)	0.43
Vaginal (n)	1.546 (74.4%)	13 (0.6%)	315 (15.1%)	18 (0.9%)	186 (8.9%)	2078 (64.5%)	0.21
Male (n)	1.197 (74.0%)	7 (0.4%)	251 (15.5%)	10 (0.6%)	152(9.4%)	1.617 (100%)	0.12
Female (n)	1.172 (72.9%)	14 (0.9%)	256 (15.9%)	13 (0.8%)	152 (9.5%)	1.607 (100%)	0.24

DISCUSSION

Physiological changes that occur during pregnancy affect the functioning of the thyroid gland and thyroid function tests. There is an increase in the production of humancohorionicgonadotropin (β-hCG) secreted from the placenta especially in the first trimester of pregnancy. Alpha subunits of hCG and TSH have similar structural properties. Due to this similar biochemical property, hCG causes stimulation of the thyroid gland by binding to TSH receptors. This increase in hCG may cause an increase of up to 50% in daily iodine need and free T4 and free T3 values, and a decrease in TSH levels (10).

It is stated that overt maternal hypothyroidism and overt maternal hyperthyroidism have negative effects on the central nervous system and neurocognitive development of the fetus and increase obstetric risks (11). Thyroid dysfunction has a relatively high prevalence during pregnancy and affects 5% of all pregnant women; most common maternal hypothyroidism (12).

The main cause of hypothyroidism in pregnancy is iodine deficiency (13). Hypothyroidism may cause neurodevelopmental disorders in neonatal and childhood (14). Routine screening is not recommended in pregnant women for hypothyroidism. Screening can be performed by thyroid function tests in the presence of radiation history, individual and familial risk factors, the age of the pregnant more than thirty or morbid obesity (15). However, our country is in an endemic position in terms of iodine deficiency. Since TSH measurement is at an acceptable cost, TSH measurement is recommended for women planning pregnancy and pregnant women at the beginning of pregnancy (5).

Subclinical hypothyroidism is a mild form of hypothyroidism common among women of childbearing age. The impact of SCH on adverse perinatal outcomes is unclear, and universal screening for thyroid function before or during pregnancy is also much discussed (16).

Many studies have been conducted on the prevalence of hyperthyroidism and pregnancy effects worldwide. In a comprehensive study conducted in China, the prevalence of subclinical hypothyroidism was 27.8%, in a cross-sectional study conducted in India, the rate of overt hypothyroidism was found to be 1.3%, the rate of subclinical hypothyroidism was found to be 21.5%, and the rate of subclinical hypothyroidism was 37% in a study conducted in Pakistan (17-18-19). In a meta-analysis study, the prevalence of general thyroid dysfunction in pregnant women in Iran was found to be 18.10%. The prevalence of hypothyroidism and subclinical hypothyroidism in pregnant women was 13.01% and 11.90%, respectively (20). In a study conducted in India, the prevalence of thyroid dysfunction was found to be 13.9% (prevalence of hypothyroidism 12.76%, prevalence of hyperthyroidism 1.13%) (21). In a study investigating the frequency of thyroid dysfunction in our country, subclinical hyperthyroidism rate was 4.16%, overt hyperthyroidism rate 1.22%, overt hypothyroidism rate 10.18%, subclinical hypothyroidism rate 5.70% (22). Another study found euthyroidism in 81.1% of patients, hyperthyroidism in 2.4%, and hypothyroidism in 16.3 % (23). In a similar study, the frequency of hyperthyroidism and hypothyroidism was 2.8% and 4.3%, respectively (24). In our study, it was obvious The rate of hyperthyroidism was 0.65%, subclinical hyperthyroidism rate 0.71%, overt hypothyroidism rate 15.6%, subclinical hypothyroidism rate 9.4%. In our study, it is seen that the frequency of overt hypothyroidism and subclinical hypothyroidism is higher, in accordance with the literatüre.

One of the most important biochemical parameters for healthy fetal development is thyroid hormone levels (25) There are studies showing that maternal thyroid dysfunction affects fetal birth weight. These studies show that maternal FT4 levels are inversely proportional to birth weight throughout pregnancy (26, 27).

According to the meta-analysis study, maternal subclinical hypothyroidism during pregnancy was associated with a higher risk of SGA and lower birth weight, while isolated hypothyroxinemia was associated with a lower risk of SGA and higher birth weight (28). Especially babies with hypothyroidism are reported to be born with lower birth weight (29). In a different study conducted in our country, it was stated that there was no significant difference between TSH level and fetal birth weight. Also, it has been stated that if TSH is detected within normal limits in the first trimester, further examinations are

not required (30). Similarly, in our study, no statistically significant difference was found between the groups and low birth weight, mode of delivery and baby gender.

It is stated that pregnant women with hypothyroidism during pregnancy have the possibility of premature birth (31-32). The meta-analysis study shows that maternal subclinical hypothyroidism is associated with fetal distress (33). Low T3 and T4 levels can be seen in preterm babies. Nonspecific findings of hypothyroidism such as hypotonia, constipation, low growth rate and low growth rate can be seen in these babies (34). On the other hand, studies are reporting that there is no difference between the prevalence of early preterm births between pregnant women with thyroid dysfunction and normal thyroid function values (35-36). In our study, no significant statistical difference was found between the groups and the week of birth.

In our study, first-trimester maternal body mass index, weight and height of the father and mother, alcohol and smoking habits, and not knowing the mother's eating habits constitute the weaknesses of our study.

CONCLUSION

In our study, a high prevalence of thyroid disease, especially hypothyroidism, was observed in pregnant women. More studies should be conducted to evaluate the effect of screening thyroid functions and treatment of thyroid disorders, especially hypothyroidism, on pregnancy outcomes.

Limitations of the study: Information on some perinatal outcomes (fetal distress, fetal growth restriction, preterm birth, stillbirth, preeclampsia, detachment, gestational diabetes mellitus frequency, number of newborns requiring intensive care) and how many patients in the group with thyroid dysfunction received medical treatment could not be obtained. In addition, the fact that anti-thyroglubulin(anti-TPO) was not tested in patients is a limitation of the study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Van Ministry of Health University Training and Research Hospital Clinical Research and Ethics Committee (Date: 07/03/2019, Decision No: 2019/05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. Obstet. Gynecol 2005; 105: 239-45.
2. Glinoer D. Thyroid regulation and dysfunction in the pregnant patient. Thyroid 2004; 14: 234-45.
3. Girling JC. Thyroid disorders in pregnancy. Curr Obstet Gynecol 2006; 16: 539-47.
4. Fisher DA. Fetal thyroid function: diagnosis and management of fetal thyroid disorders. Clin Obstet Gynecol 1997; 40: 16-31.
5. Türkiye Endokrinoloji ve Metabolizma Derneği, Tiroid Hastalıkları Tanı ve Tedavi Kılavuzu 2017.
6. Delshad H, Azizi F. Thyroid and pregnancy. J Med Counc Iran 2008; 26: 392–408.
7. Negro R, Mestman JH. Thyroid disease in pregnancy. Best Pract Res Clin Endocrinol Metab 2011; 25: 927–43.
8. Thyroid disease in pregnancy. American College of Obstetrics and Gynecology. Int J Gynaecol Obstet; 2002; 79: 171-80.
9. El Baba KA, Azar ST. Thyroid dysfunction in pregnancy. Int J Gen Med 2012; 5: 227–30.
10. Utiger RD. Maternal hypothyroidism and fetal development. N Engl J Med 1999; 341: 601.
11. Sawyer HP, Denice SF. Maternal thyroid disease and its effects on the fetus and perinatal outcomes. Prenatal diagnosis, 2020; 40: 1077-84.
12. Mulik J, Pratapan P, Agrawal N. Study of thyroid disorders in pregnancy & its effect on maternal & perinatal outcomes at a tertiary care centre. Hypertension 2019; 42: 40.
13. Cignini P, Cafà EV, Giorlandino C, Capriglione S, Spata A, Dugo N. Thyroid physiology and common diseases in pregnancy: review of literature. J Prenat Med 2012. p. 2012; 6: 64–71
14. Andersen S, Bruun NH, Pedersen KM, Laurberg P. Biologic variation is important for interpretation of thyroid function tests. Thyroid 2003; 13: 1069-78.
15. Nazarpour S, RamezaniTehrani F, Simbar M, Azizi F. Thyroid dysfunction and pregnancy outcomes. Iran J Reprod Med 2015; 13: 387–96.
16. Sun YL, Howard JC, Ann A, Elizabeth NP . Associations between maternal thyroid function in pregnancy and obstetric and perinatal outcomes. J Clin Endocrinol Metab 2020; 105: 2015-23.
17. Li C, Shan Z, Mao J, et al. Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women?. J Clin Endocrinol Metab 2014; 99: 73–9.
18. Rajput R, Goel V, Nanda S, Rajput M, Seth S. Prevalence of thyroid dysfunction among women during the first trimester of pregnancy at a tertiary care hospital in Haryana. Indian J Endocr Metab 2015; 19: 416-9.
19. Khan KA, Akhter MS, Fatima K, Saleem MW. Subclinical hypothyroidism (SCH) in first trimester of pregnancy. Prof Med J 2020; 27: 2474-7.
20. Sepasi F, Rashidian T, Shokri M, Badfar G, Kazemi F, Azami M. Thyroid dysfunction in Iranian pregnant women: a systematic review and meta-analysis. BMC Pregnancy Childbirth, 2020; 20: 1-15.

21. Korde VR, Barse SP, Barla JS. Prevalence of thyroid dysfunctions in pregnant women: a prospective study in a tertiary care hospital in Maharashtra, India. Int J Reprod Contracep Obstet Gynecol 2018, 7.8: 3211-6.
22. Güzel E, SivriAydın D, Çilesiz Göksedef BP, Boran AB. The incidence of thyroid dysfunction in pregnant women. Perinat J 2015; 23: 96-100.
23. Seven A, Kucur SK, Polat M, Yüksel B, Işıklar Ö, KeskinN. Gebelerde birinci trimester tiroid fonksiyon testi sonuçlarının değerlendirilmesi. Muğla Sıtkı Koçman Üniv Tıp Derg 2016; 2: 5-8.
24. Bulmus N, Ustuner I, Guven ESG, Sahin FK, Senturk S, Sahin SB. Thyroid diseases in pregnancy: the importance of anamnesis. Pakistan J Med Sci 2013; 29: 1187.
25. Morreale de EG, Obregon MJ, Escobar del RF. Role of thyroid hormone during early brain development. Eur J Endocrinol 2004; 151: 25-37
26. Zhang C, Yang X, Zhang Y, et al. Association between maternal thyroid hormones and birth weight at early and late pregnancy. J Clin Endocrinol Metab 2019; 104: 5853-63.
27. Johns LE, Ferguson KK, Cantonwine DE, Mukherjee B, Meeker JD, McElrath TF. Subclinical changes in maternal thyroid function parameters in pregnancy and fetal growth. J Clin Endocrinol Metab 2018; 103: 1349-58.
28. Derakhshan A, Peeters RP, Taylor PN, et al. Association of maternal thyroid function with birthweight: a systematic review and individual-participant data meta-analysis. Lancet Diabet Endocrinol 2020; 8: 501-10.
29. Alvarez-Pedrerol M, Guxens M, Mendez M, et al. Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring. Eur J Endocrinol 2009; 160: 423–9.
30. Bakacak M, Serin S, Avcı F, et al. Maternal ilk trimester tiroid stimülan hormone düzeylerinin miadında doğan fetüslerin doğum ağırlıklarına etkisi. Perinatoloji Derg 2015; 23: 79–83.
31. Poppe K, Velkeniers B, Glinoer D. The role of thyroid autoimmunity in fertility and pregnancy. Nat Clin. Pract Endocrinol Metab 2008; 4: 394–405.
32. Abalovich M, Amino N, Barbour LA, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2007; 92: 47.
33. Liu Y, Chen H, Jing CLF. The association between maternal subclinical hypothyroidism and growth, development, and childhood intelligence: a meta-analysis. J Clin Res Pediatr Endocrinol 2018; 10: 153.
34. Gönç E, Yordam N. Çocukluk ve adölesanda tiroid hastalıkları. Günöz H, Öcal, G, Yordam, N, Kurtoğlu, S. Pediatrik Endokrinoloji. 1. ed. s212-19, Kalkan Matbaacılık, Kayseri, 2003.
35. Ashoor G, Maiz N, Rotas M, Jawdat F, Nicolaides KH. Maternal thyroid function at 11–13 weeks of gestation and spontaneous preterm delivery. Obstet Gynecol 2011; 117: 293-8.
36. Günkaya OS, Kıyak H, Ekiz A, Gedikbaşı A. İlk trimesterda tiroid fonksiyonunun gebelik sonuçları. Perinatoloji Derg 2017; 25: 121–6.

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Association between vitamin D levels and frequency of disease exacerbations and hospitalizations in patients with COPD

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a debilitating disorder that restricts the physical activity of patients who are deprived of sunlight, which is a source of vitamin D. The purpose of this study was to assess the relationship between vitamin D and the frequency of exacerbation and hospitalization among patients with COPD.

Material and Method: In the main analysis, 303 patients with COPD (stage GOLD A to D) were included in a retrospective cohort study in Turkey. Serum levels of vitamin D (25-hydroxyvitamin D) were measured in 303 patients with COPD and were associated with pulmonary function, AECOPD frequency and hospitalization in the previous year. Results: For COPD patients, the mean reference level of 25 hydroxyvitamin D in serum was 12.5 ng/dL. In comparison to patients with a serious 25-hydroxyvitamin D deficiency (< 10 ng/dL, n=119 [39,3%]), patients with a moderate deficiency (10-19.99 ng/dL, n=100 [33%]), inadequate levels (20-29.99 ng/dL, n=49 [16,2%]) presented a different risk of exacerbation (incidence rate ratio, 2.3 [95% CI, 1.9-2.6], 1.6 [95% CI, 1.2-2.0], and 0.8 [95% CI, 0.3-1.2] respectively). In patients with desirable levels (> 30 ng/dL, n=34 [11,2%]), the risk was lower but not significant (incidence ratio, 0.7 [95% CI, 0.2-1.2]. In COPD patients, 25-hydroxyvitamin D rates are low correlated with 1-s forced expiratory volume (FEV1) (r=0.187, p=0.0013).

Conclusion: 25-hydroxyvitamin D deficiency is a frequent occurrence in COPD and is correlated with the frequency of exacerbation and hospitalization in COPD patients.

Keywords: 25-hydroxyvitamin D, COPD, COPD exacerbation

INTRODUCTION

COPD is a big public health threat and the fourth cause of mortality worldwide (1). COPD progression varies greatly among affected individuals, both in terms of lung function decrease (2) and exacerbation frequency (3). COPD is a chronic and progressive illness characterized by periods of exacerbation associated with reduced health-related quality of life, increased use of health resources, and increased mortality (4). Acute exacerbations of COPD requiring hospitalization are especially important because they cause an economic burden and threaten the life of the affected patients (5).

Cross-sectional studies have shown that 25-hydroxyvitamin D deficiency is widespread in patients with COPD, and that it is associated with lower lung function in patients with COPD (6-8). Some investigators found a link between 25-hydroxyvitamin D levels and the risk of COPD and the severity of the disease in patients with COPD (9). While this is true, it can be explained by systemic and pulmonary immunomodulatory effects of 25-hydroxyvitamin D (10,11). Laboratory studies have revealed an extensive range of immunomodulatory effects of 25-hydroxyvitamin D in the lungs. that maintain immune system activity to fight microbial pathogens and inflammation (12,13). As a result, 25-hydroxyvitamin D deficiency can increase chronic and systemic inflammation of the respiratory tract, decrease bacterial clearance and increase the risk of infectious exacerbations (14). However, these results are not conclusive. There have been few studies of 25-hydroxyvitamin D function in COPD patients, and one of them did not show any association between 25-hydroxyvitamin D and impaired lung function or exacerbation (15). The relationship between 25-hydroxyvitamin D deficiency and the frequency of exacerbation in observational studies remains controversial; however, a meta-analysis

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(including some of the available studies which did not find any association) showed a negative association between serum 25-hydroxyvitamin D and exacerbation frequency (9).

It is not clear whether 25-hydroxyvitamin D deficiency is more widespread among COPD patients than among the general population of Turkey. Whether patients with COPD with diverse 25-hydroxyvitamin D levels experience different exacerbation frequencies is unknown. In addition, 25-hydroxyvitamin D levels at different COPD stages have not been studied. The aim of this retrospective study was to evaluate the possible role of serum 25-hydroxyvitamin D as a predictor of airway obstruction (FEV1), frequency of exacerbation, hospitalization, and results of MCRC scores in patients with COPD.

MATERIAL AND METHOD

The study was initiated with the approval of the Keçiören Training and Research Hospital Ethics Committee (Date: 23.11.2021, Decision No: 15-2409). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

Study Design and Population

We retrospectively collected electronic medical records at the Ataturk Chest Disease Hospital in Ankara (Turkey) from January 2018 to December 2019. Participants will be enrolled if they present with COPD exacerbation to the outpatient clinic or emergency department. We included patients suspected of having COPD based on their clinical history and meeting the GOLD criteria for COPD 16 as cases in the study. The inclusion criteria were the following: 1) Spirometry results displaying a forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) < 0.7 after bronchodilator therapy; and 2), smoking history of ≥ 10 pack-year; absence of vitamin D oral supplementation, and an increased frequency of Acute Exacerbation Chronic Obstructive Lung Disease (AECOPD) in the subsequent year. All records were retrospectively screened.

We described COPD exacerbations as a sustained aggravation of respiratory symptoms over a 48-hour period, requiring an oral corticosteroid, an antibiotic, or a combination of treatments initiated by a doctor. Respiratory symptoms included one or more of the Anthonisen criteria (increase in dyspnea, volume of sputum, or purulence of sputum) with or without minor symptoms (such as fever, coughing, wheezing, common cold symptoms, or sore throat). We assessed the severity of the patients' dyspnea according to the results of a modified Medical Research Council (mMRC) scale questionnaire applied in the outpatient clinic.

The exclusion criteria included a diagnosis of asthma or some other disease such as tuberculosis, bronchial carcinoma, sarcoidosis, kidney or liver failure (creatinine, > 1.5 mg/dl and estimated creatinine clearance, 20 ml/min) or bronchiectasis, or the use of active metabolites.

Measurement of 25-Hydroxyvitamin D

Serum screening concentration 25-hydroxyvitamin D will be measured within the exacerbation period. We classified 25-hydroxyvitamin D levels as normal (≥ 30 ng/ml), mild to moderately deficient (≥ 10, but < 30 ng/ml), or severely deficient (< 10 ng/ml) (17).

Covariates included characteristics potentially associated with 25-hydroxyvitamin D state and AECOPD risk (such as age, sex, percentage of expected FEV1, season [winter ¼, Jan-Mar; spring ¼, Apr-Jun; summer ¼, Jul-Sept; winter ¼, Oct-Dec) clinical center. .

Study design

In the original study, we allocated 303 patients into either a low (< 30 ng/dl, n=270) or the high (≥ 30 ng/dl, n=33) 25-hydroxyvitamin D level group according to their 25-hydroxyvitamin D level measured at the emergency/hospital admission. In the course of the analysis, the following parameters were compared between the two groups over one year after initial hospital care: number of exacerbations per patient-year; number of hospital days per patient-year.

STATISTICAL ANALYSIS

The Pearson chi-square test was used for comparing the prevalence of categorical variables between groups (two or more groups). Once we have determined the distribution of continuous variables, we present normally distributed variables as means±SD and non-normally distributed variables as medians (IQR).

We applied a t-test or Mann-Whitney-test to compare differences in the differences in continuous variable levels between the two groups (e.g., men vs. women or individuals with or without severe 25-hydroxyvitamin D deficiency). We assessed how the level-25-OH-VitD3 reference plasma affected exacerbations using the Chi-Square test considering that the variable (exacerbation frequency) is dichromatic.

Linear regression analyses were conducted to analyze the association between 25-hydroxyvitamin D (log-transformed) levels and rates of exacerbation. These associations have been tested in multiple linear regression models with adjustments to take into account possible confounding factors. We considered a two-tailed $p < 0.05$ as statistically significant.

RESULTS

We enrolled 303 cases in this study. Their mean±SD age was 66,1±8,3 years (median, 66 years; range, 44–88 years); their FEV1 median, 39% (ICQ 26–54%); and their level of dyspnea median (modified Medical Research Council scale level) 2 (ICQ 2-3; range, 0–4). According to the GOLD stages, 40 (13,2%), 96 (31,7%) and 167 (55,1%) patients were categorized into GOLD class A, B, and D, respectively.

The mean concentration for 25-hydroxyvitamin D was 12.5 ng/dL (IQR, 8.08–20,9 ng/dL), and 270 patients (88.4%) were 25-hydroxyvitamin D deficient (< 30 ng/dL). In total, 16.2% were deficient in 25-hydroxyvitamin D (definition > 20 ng/ml but < 30 ng/ml according to widely used criteria)17); 72.6% were deficient in 25-hydroxyvitamin D (< 20 ng/ml); and 39.3% were severely deficient in 25-hydroxyvitamin D (< 10 ng/ml) (**Table 1**).

Table 1. Baseline characteristics ,pulmonary fuction and clinical characteristics of non-deficiency and deficiency groups of with COPD

Parameters	Non-Deficiency (n=33)	Deficiency (n=270)	P-Value
Age, years	69.6±7,1	66,6±8,6	0.053
Gender, m/f	31/2	226/44	0.038
GOLD A	10	28	
GOLD B	13	84	
GOLD D	10	158	
FEV1,% predectid	41 (IQR 25.5-48)	39 (IQR 26-54)	0.93
Baselinde plasma 25OH D vit	36.5 (IQR33.7-47.3)	11.1 (IQR 7.7-17.9)	0.0001
AECOPD (y/n)%	18.2(%)	45,2(%)	0.003
Number of mean AECOPD/ year	0,72±1,35	1,8±1,98	0,001
Hospitalization(y/n)%	24.2(%)	43.3(%)	0.03

There were significant sex differences across groups. The percentage of predicted FEV1 (39% vs 41%; P=0.93) was higher in the non-deficiency than in the deficiency group. Serum circulating 25-hydroxyvitamin D rates were weakly correlated with FEV1 in the COPD sub-group. (Pearson r=0.187, p=0.0013; **Figure 1**).

In patients with COPD, we found that 25-hydroxyvitamin D levels were significantly associated with the combined severity of the COPD stage. (**Figure 2**). Thirty-three (10.9%) of the patients had adequate serum 25-hydroxyvitamin D concentrations (≥30 ng/mL), while the remaining 270 (89.1%) were deficient in 25-hydroxyvitamin D (<30 ng/mL). Taken as a whole, this data clearly indicates that the reduction in 25-hydroxyvitamin D levels is correlated with the mMRC, exacerbation frequency, and COPD hospitalizations.

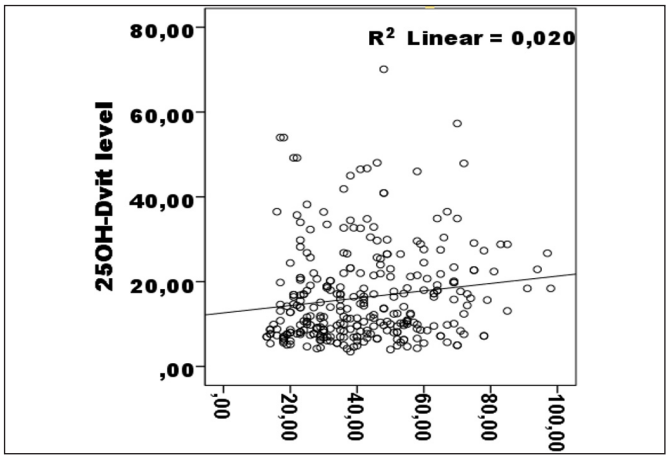

Figure 1. Correlation with D vit level and FEV1

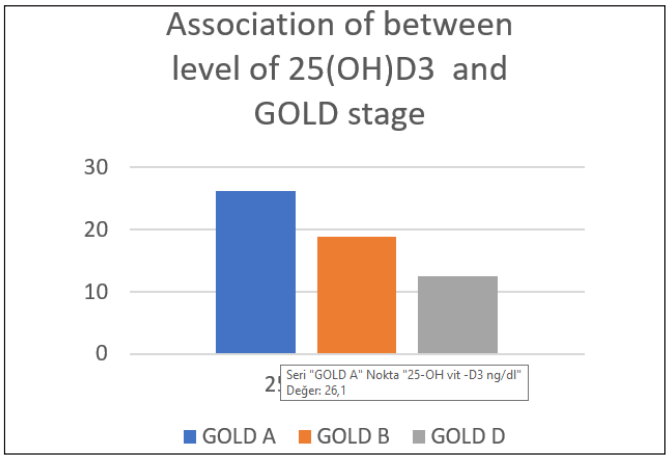

Figure 2: This figure showing 25-OHD levels according to the various GOLD (Global Initiative for Obstructive Lung Disease) stages. Serum 25(OH) D concentration among different grades of COPD (n= 37 for patients A group=98 for patients grade B COPD ; n=168 for patients with grade D COPD). All data were represented as mean ± SEM. *p<0.001

Association of 25-hydroxyvitamin D with Exacerbations and Hospitalization

In all, 181 participants experienced 493 AECOPDs over one year. A total of 122 participants (40.3%) remained AECOPD-free over one year; 53 (17.5%) had one AECOPD; 47 (15.5%) had two AECOPDs; and 81 (67%) had three or more AECOPDs.

The proportion of participants who were severely deficient in 25-hydroxyvitamin D increased with the number of AECOPDs (p < 0.001) (**Figure 3**).

Importantly, the levels of serum 25-hydroxyvitamin D were significantly higher in patients with COPD who had at least one exacerbation-related hospitalization than in those who had not been hospitalized . (**Figure 4**). Serum levels of vitamin 25-hydroxyvitamin D were associated with dyspnea perception on the mMRC scale (**Figure 5**).

The prevalence of severe 25-hydroxyvitamin D deficiencies was highest in frequent patients compared to those without frequent exacerbations. (55.5% vs. 27.4%, p<0.001).

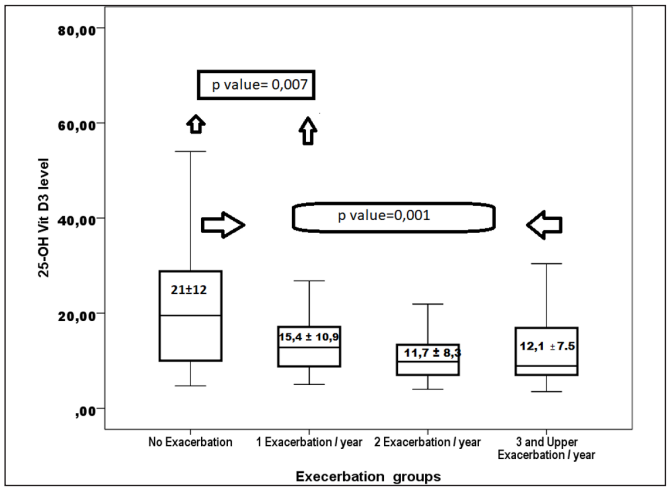

Figure 3. This figure showing 25-OHD levels according to the various GOLD (Global Initiative for Obstructive Lung Disease) stages. Serum 25(OH) D concentration among different grades of COPD (n= 37 for patients A group=98 for patients grade B COPD ; n=168 for patients with grade D COPD). All data were represented as mean ± SEM. *p<0.001

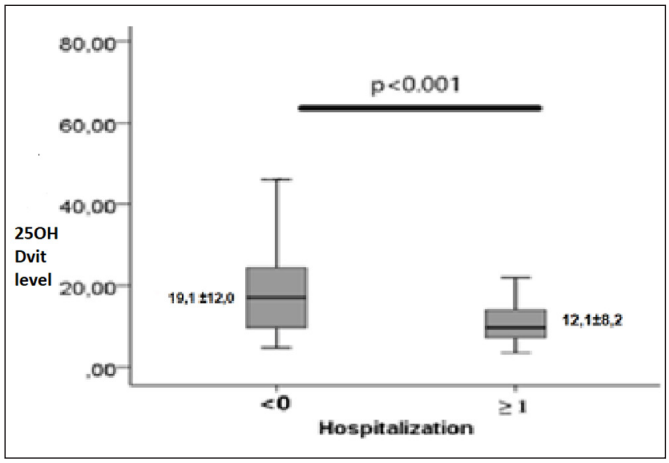

Figure 4. Comparison of serum 25-OH D3 vit concentration in COPD patients with ≥ 1 hospitalized exacerbation and those who were not hospitalized. The central horizontal line on each box represents the median, the ends of the boxes are 25 and 75 percentiles and error %5 and 95%. P values derived from the Mann -Whitney U test

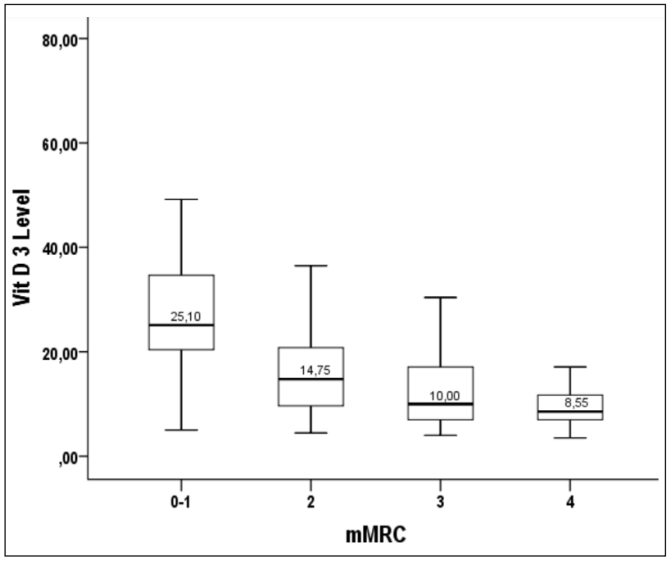

Figure 5. Serum levels of vitamin 25-OH D3 were associated with dyspnea perception on the mMRC scale

The mean number of exacerbations over one year were 2.3±2.1, 1.6±1.8, 0.8±1.6, and 0.7±1.3 in the patients with 25-hydroxyvitamin D concentrations of < 10 ng/dL, 10 ng/dL to 19.99 ng/dL, 20 ng/dL to 29.99 ng/dL, and > 30 ng/dL, respectively.

An analysis of AECOPD levels stratified according to 25-hydroxyvitamin D levels showed that participants with severe 25-hydroxyvitamin D deficiency (<10 ng/ml) had a higher average AECOPD rate than the others. The discrepancy is statistically significant. (p=0.001).

DISCUSSION

In our research, we found that the serum 25-hydroxyvitamin D levels were associated with important clinical correlates of COPD such as the exacerbation frequency, the mMRC symptom scales, and the hospitalization frequency score. Most importantly, Serum levels of 25-hydroxyvitamin D were significantly reduced in patients with COPD who had experienced at least one exacerbation in the previous year. Severe deficiency of 25-hydroxyvitamin D was associated with frequent exacerbations the following year, as documented in our clinic. We also showed that measures of 25-hydroxyvitamin D levels can provide a predictive tool for evaluating the frequency of exacerbations associated with hospitalizations in COPD patients.

However, the association of serum 25-hydroxyvitamin D levels with the frequency of exacerbation is uncertain (18). Our results are consistent with research done by Sanket et al. (19) which have shown COPD to be associated with an increased risk for 25-hydroxyvitamin D deficiency. A meta-analysis by Zhu et al. (9) found no associations. Zhu et al. (9) studied the association between serum levels of 25 hydroxyvitamin D in the host and the severity of COPD and found that low serum levels of 25-hydroxyvitamin D were not associated with sensitivity to COPD but high deficiency rate 25-hydroxyvitamin D had been linked to the severity of COPD. Indeed, two studies have shown 25-hydroxyvitamin D deficiency to be associated with more frequent exacerbations (20,21) while others have not found this association (15,22,23). The relationship between 25-hydroxyvitamin D deficit and exacerbation of COPD is controversial. Puhan et al. (23) informed a trend whereby patients suffering from severe 25-hydroxyvitamin D deficiency were sensitive to exacerbations without statistically significant relationship. Martineau et al. (24) recommended that 25-hydroxyvitamin D supplementation was protective of moderate to severe exacerbation in COPD patients with 25-hydroxyvitamin D deficiency. In our study, we found a retrospective cohort in which severe 25-hydroxyvitamin D deficiency (<10 nmol/L) was associated with more frequent exacerbation of COPD in the year preceding 25-hydroxyvitamin D measurements. A longitudinal study by Persson et al. (25)

showed that patients with COPD and hypovitaminosis D. (< 50 nmol/L, n=142) had more severe COPD, and more frequent exacerbations.

There are several mechanisms that can explain the contribution of 25-hydroxyvitamin D deficiency to COPD exacerbation. First, VDR (25-hydroxyvitamin D receptor) dysfunction, dependent on 25-OH D deficiency, is thought to decrease the innate immune function which increases the susceptibility to infections (26). Also, airway epithelial and immune cells in the lung express VDR. Other researchers have found higher levels of vitamin D3-binding proteins in COPD patients. associated with macrophage activation and neutrophil chemotaxis (underlying COPD pathogenesis mechanisms). A dysregulated immune-inflammatory response causes chronic inflammation and lung structural destruction. Secondly, 25-hydroxyvitamin D may regulate the expression of antimicrobial peptides as a response to infections (27,28). Quint et al. (22) noticed that the 25-hydroxyvitamin D deficiency is associated with COPD and increased susceptibility to infections among the general population. 25-hydroxyvitamin D deficiency can help initiate bacterial or viral infections and lead to acute COPD exacerbations. Exacerbations are predominantly initiated by infections, and patients with frequent exacerbations have impaired daily activities, spend less time outdoors (29), have rapid disease progression (30), and present a higher mortality rate (31) than patients with infrequent exacerbations.

NHANES III research has shown an inverse dose-response relationship between 25-hydroxyvitamin D levels and upper respiratory tract infections in asthmatics., and a similar association was observed for COPD cases (although not significant after adjustments) (32). In this study, we found a link between exacerbation frequencies and measured 25-hydroxyvitamin D levels. According to our research results, patients with 25-hydroxyvitamin D deficiency (<10 nmol/L) had the highest risk for exacerbations (2.3±2.1 exacerbations per year), suggesting the deficiency is a risk factor for exacerbations.

In our research, we found a low correlation between 25-hydroxyvitamin D levels and lung function tests. The Third National Health And Nutritional Exam Survey in the United States United has shown that the difference between the highest and lowest quintiles of 25-hydroxyvitamin D was greater in people diagnosed with emphysema or chronic bronchitis than in others, which suggests a stronger association between 25-hydroxyvitamin D and FEV1 levels in COPD patients compared to the general population (33). In a previous study on patients with COPD by Janssens et al. (13) they found that a strong association between the GOLD stage and the presence of 25-hydroxyvitamin D deficiency suggested the presence of airway obstruction. These researchers suggested the existence of a strong association between 25-hydroxyvitamin D and COPD. However, our study could not find a similarly strong correlation between FEV1 and 25-hydroxyvitamin D levels. Based on our results, the exacerbation and hospitalization frequencies are good predictors of deficient 25-hydroxyvitamin D levels. Thus, the fact that these 25-hydroxyvitamin D levels were associated with AECOPD exacerbation or hospitalization rates suggests that serum 25-hydroxyvitamin D can be used to predict risk of future exacerbations in COPD patients. Possible explanations include the fact that 25-hydroxyvitamin D has been involved in tissue remodeling via collagen synthesis and fibroblast proliferation, and modulation of matrix metalloproteinase levels (34). In addition, undiagnosed osteoporosis resulting in spinal compressions can result in loss of height, decreased thoracic mobility and reduced lung function (35). In an article by Black et al. (33), 25-hydroxyvitamin D levels were strongly associated with FEV1 and FVC, with standardized data for sex, age, ethnic origin, smoking history and body mass index (BMI).

Patients with COPD experience increased skin aging due to smoking and decreased sun exposure due to restrictions on outdoor activities, and these conditions lead to reduced 25-hydroxyvitamin D serum levels (13). Patients with COPD are frequently treated with corticosteroids, which increase vitamin D catabolism.

In our study, there was a statistically significant difference in 25-hydroxyvitamin D levels in male. (16.7±11.2) and female (13.8±10.3) with COPD, similar to the results of previous studies (**Table 2**). For example, Black et al. (14) reviewed the information from the NHANES III research undertaken in the USA on 14, 091 individuals and female were found to have significantly lower average levels of 25-hydroxyvitamin D compared to men (28.72 ng/mL versus 31.37 ng/mL). It was suggested that these results could be attributed to women's preference for clothing. that covered most of their body for religious reasons, or due to the use of sun creams for cosmetic reasons or for skin cancer protection.

Table 2. Coefficients from multiple linear regression and logistic regression models ,showing the relationship between baseline predictors and serum levels of 25(OH)D3(<30 mg/dl) in COPD patients

Risk factor	RR (%95 CI)	P value
Age	1.03 (0.99-1.09)	0.03
Gender	2.6 (0.58-11.9)	0.20
Season		
Autumn	2.6(0.8-8.1)	0.08
Winter	0.5(0.1-2.9)	0.50
Spring	1.8(0.7-4.8)	0.19
Summer		
Exacerbation frequency(y/n)	4.0(1.6-10.2)	0.003

For the both linear and lositic regression models a backward stepwise procedure was used the fallowing variables include at start: age,sex,season and exacerbation (yes/no)

Seasonality, as a confounding factor, can influence overall study results. Several researchers have demonstrated that seasonality affects 25-hydroxyvitamin D levels, but we did not find a similar phenomenon (7) (**Table 3**). Therefore, the seasons did not influence on 25-hydroxyvitamin D levels in our research.

Table 3. Seasonal variatioon of baseline plasma 25-OH VitD3 levels

Season	n	Median(IQR %25-75), ng/mL	P-value
September-November	103	10.2 (IOR 7.1- 17.2)	0,052[1]
December-Febraury	45	12.7 (IOR 7.8- 23.4)	
March-May	43	11.4 (IOR 8.6- 17.9)	
June-November	112	15.8 (IOR 8.6- 23.3)	

SD, standart deviation.1: There is not significant statistical diffrence beetwen season and plasma 25-OH VitD3 levels(p value=0,052). ANOVA used for variation with season.

The major weakness of this study is its retrospective design. Secondly since we chose to focus on 25-hydroxyvitamin D effects on AECOPD patients with 25-hydroxyvitamin D defiency, our results could not be generalized to all AECOPD patients. There are other limitations: a relatively small patient population; a failure to include all possible factors affecting 25-hydroxyvitamin D levels in individuals (Like nutrition, sunlight exposure time, and clothing style.); a failure to apply a food frequency questionnaire; and a failure to account for seasonality.

CONCLUSION

Our research findings confirm that 25-hydroxyvitamin D deficiency is associated with the severity of COPD. According to our results, Vitamin D deficiency was significantly related to higher rates of exacerbation and hospitalization for COPD. Larger clinical trials with similar evidence is needed to make conclusions about the link between 25-hydroxyvitamin D and the risk of exacerbation. Further research is needed to identify the benefits of the strategies aimed at preventing COPD exacerbations, including the use of vitamin D supplementation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Keçiören Training and Research Hospital Ethics Committee (Date: 23.11.2021, Decision No: 15-2409).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Lopez A, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006; 27: 397-412.
2. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. New Engl J Med 2011; 365: 1184-92.
3. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. New Engl J Med 2010; 363: 1128-38.
4. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187: 347-65.
5. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet (London, England) 2007; 370: 765-73.
6. Janssens W, Bouillon R, Claes B, et al. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax 2010; 65: 215-20.
7. Persson LJP, Aanerud M, Hiemstra PS, Hardie JA, Bakke PS, Eagan TML. Chronic obstructive pulmonary disease is associated with low levels of vitamin D. PloS one 2012; 7.
8. Romme EA, Rutten EP, Smeenk FW, Spruit MA, Menheere PP, Wouters EF. Vitamin D status is associated with bone mineral density and functional exercise capacity in patients with chronic obstructive pulmonary disease. Ann Med 2013; 45: 91-6.
9. Zhu M, Wang T, Wang C, Ji Y. The association between vitamin D and COPD risk, severity, and exacerbation: an updated systematic review and meta-analysis. Int J Chron Obstructive Pulmonary Dis 2016; 11: 2597.
10. Janssens W, Mathieu C, Boonen S, Decramer M. Vitamin D deficiency and chronic obstructive pulmonary disease: a vicious circle. Vitamins Hormones 2011; 86: 379-99.
11. Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J Immunol 2008; 181: 7090-9.
12. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 311: 1770-3.
13. Janssens W, Lehouck A, Carremans C, Bouillon R, Mathieu C, Decramer M. Vitamin D beyond bones in chronic obstructive pulmonary disease: time to act. Am J Respir Crit Care Med 2009; 179: 630-6.
14. Zasloff M. Fighting infections with vitamin D. Nature medicine 2006; 12: 388-90.
15. Kunisaki KM, Niewoehner DE, Connett JE. Vitamin D levels and risk of acute exacerbations of chronic obstructive pulmonary disease: a prospective cohort study. Am J Respir Crit Care Med 2012; 185: 286-90.
16. Singh D, Agusti A, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J 2019; 53.
17. Holick MF. Vitamin D deficiency. New Engl J Med 2007; 357: 266-81.
18. Ferrari R, Caram LM, Tanni SE, Godoy I, de Paiva SAR. The relationship between Vitamin D status and exacerbation in COPD patients–a literature review. Respir Med 2018; 139: 34-8.

19. Sanket S, Madireddi J, Stanley W, Sura P, Prabhu M. Relation between vitamin D deficiency and severity of chronic obstructive pulmonary disease-A case control study. JCDR 2016; 10: OC16.
20. Malinovschi A, Masoero M, Bellocchia M, et al. Severe vitamin D deficiency is associated with frequent exacerbations and hospitalization in COPD patients. Respir Res 2014; 15: 131.
21. Mekov E, Slavova Y, Tsakova A, et al. Vitamin D deficiency and insufficiency in hospitalized COPD patients. PLoS One 2015; 10.
22. Quint JK, Donaldson GC, Wassef N, Hurst JR, Thomas M, Wedzicha JA. 25-hydroxyvitamin D deficiency, exacerbation frequency and human rhinovirus exacerbations in chronic obstructive pulmonary disease. BMC Pulmonary Med 2012; 12: 28.
23. Puhan MA, Siebeling L, Frei A, Zoller M, Bischoff-Ferrari H, Ter Riet G. No association of 25-hydroxyvitamin D with exacerbations in primary care patients with COPD. Chest 2014; 145: 37-43.
24. Martineau AR, James WY, Hooper RL, et al. Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med 2015; 3: 120-30.
25. Persson LJ, Aanerud M, Hiemstra PS, et al. Vitamin D, vitamin D binding protein, and longitudinal outcomes in COPD. PloS one 2015; 10.
26. Wei R, Christakos S. Mechanisms underlying the regulation of innate and adaptive immunity by vitamin D. Nutrients 2015; 7: 8251-60.
27. Gombart AF. The vitamin D–antimicrobial peptide pathway and its role in protection against infection. Future Microbiol 2009; 4: 1151-65.
28. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients 2015; 7: 4240-70.
29. Donaldson GC, Wilkinson TM, Hurst JR, Perera WR, Wedzicha JA. Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005; 171: 446-52.
30. Donaldson G, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002; 57: 847-52.
31. Soler-Cataluna J, Martínez-García MÁ, Sánchez PR, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005; 60: 925-31.
32. Ginde AA, Mansbach JM, Camargo CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 2009; 169: 384-90.
33. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. Chest 2005; 128: 3792-8.
34. Timms P, Mannan N, Hitman G, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM 2002; 95: 787-96.
35. Schlaich C, Minne H, Bruckner T, et al. Reduced pulmonary function in patients with spinal osteoporotic fractures. Osteoporosis International 1998; 8: 261-7.

Original Article

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Comparison of demographic and laboratory data of young and elderly patients who deceased due to COVID-19

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ABSTRACT

Introduction: Differences between young and elderly patients who deceased due to COVID-19 require further elucidation. The present study aimed to compare the differences between young and elderly patients who died from COVID-19.

Material and Method: In this single-center cross-sectional study, patients included who had been diagnosed with COVID-19 and had died in the course of hospital follow-up. The following data were recorded. Demographic characteristics of the patients, date of diagnosis, length of diagnosis to death, the first place of hospitalization, duration of hospitalization at the clinical service and intensive care unit, blood parameters. Patients included in the study were divided into 2 groups, i.e., patients aged <65 and ≥65 years, and the relationship between the study data and these two groups were examined.

Results: We included 369 patients. Prevalence of comorbid chronic diseases was significantly higher in the ≥65 years group (81.3% vs. 90.1%, p = 0.034). Prevalence of hypertension and chronic obstructive pulmonary disease was higher in the ≥65 years group (respectively, 72% vs. 84.4%, p = 0.013; 10.7% vs. 30.6%, p < 0.001). Intergroup comparison of laboratory parameters indicated that alanine aminotransferase and lactate dehydrogenase levels were higher in the <65 years group (respectively, p = 0.004; p = 0.020), whereas the creatinine levels were higher in the ≥65 years group (p < 0.001).

Conclusion: This study captured the comorbidities, laboratory parameters, and duration of hospitalization of young and elderly patients, who died due to COVID-19. In the light of the study data, there was no significant intergroup difference.

Keywords: SARS-CoV-2, elderly, young, comorbidity, hematological test

INTRODUCTION

Since December 2019, there is an outbreak of a novel coronavirus infectious disease (COVID-19) that first emerged in China and spread thereafter to the entire world (1). The virus is a RNA virus and it has become a major public concern after epidemic of Severe Acute Respiratory Syndrome-CoV (SARS-CoV), and was named Severe Acute Respiratory Syndrome-CoV-2 (SARS-CoV-2) (2). Studies showed that SARS-CoV-2 is close to beta-coronaviruses family and like other coronaviruses, the SARS-CoV-2 has a positive-sense single-stranded RNA (3). Common clinical symptoms of the disease include fever, dry cough, fatigue, myalgia, shortness of breath, normal or decreased leukocyte counts, and radiographic pneumonia (4-7). A number of studies showed that age and comorbidities, including hypertension (HT) and chronic heart disease, were risk factors for a higher rate of mortality in patients with COVID-19 (8). A study described the clinical features of young and elderly patients who died due to COVID-19 and suggested that the likelihood of acute heart damage was higher in the middle-aged, and younger patients (9-11). Differences between young and elderly patients who died due to COVID-19, are still not fully known.

The present study aimed to compare the differences between young and elderly patients who died from COVID-19.

MATERIAL AND METHOD

Study Design

The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 18.11.2021, Decision No: 2021/719). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was designed as a single-center cross-sectional study.

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Patient Enrollment

Patients, aged >18 years, who had been diagnosed with COVID-19 through the Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) test and had subsequently died in the course of the hospital follow-up, between 01.04.2020 and 13.01.2021 were included in the study. Exclusion criteria were a negative RT-PCR result, pregnancy, and age of <18 years.

Data Collection

Patient data were retrieved from the hospital information system. Data retrieved from electronic medical records were then captured on a standardized form. Patient age, sex, comorbid diseases, diagnosis (RT-PCR positive), length of hospitalization, length of diagnosis to death, admission place, total duration of hospitalization, duration of stay at clinical service, and duration of stay at the intensive care unit (ICU) were recorded. Furthermore, the system-related biochemical parameters, including coagulation parameters, kidney, and liver function tests, and hemogram parameters were recorded. The laboratory parameters that were used in the study were acquired from the tests conducted at the time of the patients' admission to the emergency medicine department.

Patients included in the study were divided into 2 groups according to their age, i.e., <65- and ≥65- year groups. The relationship between the duration of stay, time to death, comorbidities, and laboratory parameters were statistically compared between these two groups.

Statistical Analysis

The study data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) Version 20.0. The normality hypothesis for the distributions of continuous variables was tested via the Shapiro–Wilk test. Data were presented as mean±standard deviation or median (min-max), as appropriate. Additionally, the intergroup differences were compared using the Student's t or Mann–Whitney U-test, as appropriate. Categorical data were analyzed by Pearson's chi-squared test. Statistical significance was indicated by $p < 0.05$.

RESULTS

Among the 381 patients initially included in the study, 12 were excluded owing to a lack of data. Therefore, the study was performed using data of 369 patients (159 [43.1%] women and 210 [56.9%] men). The patients' mean age at death was 73.62±12.19 years. The demographic characteristics and laboratory parameters of the patients included in the study are summarized in **Table 1**.

Prevalence of comorbid chronic diseases was significantly higher in the ≥65-year group (81.3% vs. 90.1%, $p = 0.034$). Furthermore, the prevalence of hypertension (HT) and chronic obstructive pulmonary disease (COPD) was higher in the ≥65 years group (respectively, 72% vs. 84.4%, $p = 0.013$; 10.7% vs. 30.6%, $p < 0.001$). There was no significant intergroup difference in terms of the total duration of hospitalization and clinical service stay, time from diagnosis to death (respectively, 12 vs. 11 days, $p = 0.269$; 3 vs. 3.5 days, $p = 0.218$; 14 vs 14.5 days $p=0.854$), nevertheless, the duration of ICU stay was longer in the <65-years group (6 vs. 4 days, $p = 0.028$). Intergroup comparison of the laboratory parameters indicated that alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) levels were higher in the <65-years group (respectively, $p = 0.004$; $p = 0.020$). However, the creatinine levels were higher in the ≥65-years group ($p < 0.001$), no significant intergroup difference was noted in the other recorded parameters (ferritin, c-reactive protein (CRP), d-dimer, lower lymphocyte levels, troponin, and other parameters) ($p > 0,05$) (**Table 1**).

DISCUSSION

Data recorded since December 2019 on COVID-19 has paved the way for taking key steps to elucidate the pathophysiological and clinical features of the disease. We believe that the present study contributes to the relevant literature by comparing the demographic and laboratory data of the patients who died due to COVID-19 according to age groups.

Previous studies suggested that COVID-19 was a dangerous disease with high rates of fatality not only in the elderly patients but also in the middle-aged patient group (12-14). Since the very beginning, the researchers focused on identifying the conditions that could be considered as risk factors for mortality. Despite differences reported in the published studies, advanced age, HT, cardiovascular diseases, diabetes mellitus, and COPD were identified as high-risk factors for mortality (15-17). In the present study, the prevalence of comorbidities in all the age groups was 88.3%, while that of COPD was 81.8%. An intergroup comparison indicated the presence of statistical significance in terms of comorbid diseases and especially HT and COPD. Although consistent with the literature, this can be explained by the increase in the rate of comorbidities with advanced ages.

Elevated ferritin, c-reactive protein (CRP), d-dimer, lower lymphocyte levels, and troponin parameters can be utilized for risk stratification in severe and fatal COVID-19 cases (18-20). However, a number of relevant studies compared mild–moderate–severe COVID-19 cases. In the present study, both study groups comprised of patients who died due to COVID-19 in the course of the follow-up. The ALT and LDH levels were statistically significantly higher in patients aged <65 years, whereas the creatinine values were significantly higher in the ≥65

years group. This differentiates the present study from other studies in the literature.

In our study, no difference was noted in terms of the total duration of hospitalization, whereas the length of stay at ICU was higher in the <65-years group. On the contrary, Al-Omari et al. found that younger patients' length of stay in hospital is lesser than elderly patients. But this study was conducted with non-ICU patients and patients were divided into 3 subgroups (18-50, 50-60, bigger than 60 years) (21). This can be explained by the fact that younger patients could more easily achieve the pro-inflammation-anti-inflammation balance and that they were healthier than the elderly patients in biochemical, cytological, and endocrinological terms. Also, we performed our study on all patient groups (ward, ICU). However, the outcome was still mortality.

Our study has limitations. We didn't calculate prognosis scores such as APACHE II, SAPS II in our study due to the lack of patients' data who deceased in the ward. The study does not encompass the period after vaccination, so different results may be obtained in studies to be conducted during this period.

Table 1. Comparison between <65 years old and ≥65 years old patient

Variables	Total n (%) 369	<65 years old n(%) 75 (20.3)	≥65 years old n(%) 294 (79.7)	p value
Male sex, n (%)	210 (56.9)	39 (52)	171 (58.2)	0.336
Chronic diseases, n (%)	326 (88.3)	61 (81.3)	265 (90.1)	0.034
Diabetes mellitus	154 (41.7)	32 (42.7)	122 (41.5)	0.854
Coronary artery disease	14 (3.8)	4 (5.3)	10 (3.4)	0.496
Hypertension	302 (81.8)	54 (72)	248 (84.4)	0.013
COPD	98 (26.6)	8 (10.7)	90 (30.6)	<0.001
Asthma	45 (12.2)	14 (18.7)	31 (10.5)	0.055
Chronic renal failure	65 (17.6)	8 (10.7)	57 (19.4)	0.077
Cerebrovascular disease	23 (6.2)	14 (18.7)	87 (29.6)	0.058
Malignancy	101 (27.4)	6 (8)	17 (5.8)	0.434
Time from diagnosis to hospitalization, median (IQR)	1 (4)	1 (4)	1 (4)	0.923
Admission place, n (%)				
Isolation ward	254 (68.8)	49 (65.3)	205 (69.7)	0.463
Intensive care unit	115 (31.2)	26 (34.7)	89 (30.3)	
Time from diagnosis to death, median (IQR)	14 (13)	14 (14)	14.5 (12)	0.854
Total length of stay in hospital, median (IQR)	11 (11)	12 (13)	11 (11)	0.269
Length of stay in isolation ward	3 (9)	3 (7)	3.5 (10)	0.218
Length of stay in intensive care unit	5 (11)	6 (13)	4 (10)	0.028
Hematological Test				
D-dimer, µg/mL, median (IQR)	1.43 (2.71)	1.34 (1.57)	1.46 (2.88)	0.089
Ferritin, , ng/mL, median (IQR)	488.9 (684.7)	468 (674)	491 (686)	0.264
C-reactive protein, mg/L, median (IQR)	120.1 (142.7)	110 (142)	126 (148)	0.442
ALT, u/L, median (IQR)	25 (25)	31 (29)	24 (22)	0.004
AST, u/L, median (IQR)	39 (37)	46 (45)	38 (35)	0.162
Total Bilirubin, mg/dL, median (IQR)	0.5 (0.4)	0.4 (0.4)	0.5 (0.3)	0.301
İndirekt Bilirubin, mg/dL, median (IQR)	0.3 (0.2)	0.3 (0.27)	0.3 (0.2)	0.787
aPTT, sn, mean±SD	34.97±12.64	32.54±14.63	35.66±12.01	0.696
INR, mean±SD	1.25±0.57	1.2±0.31	1.27±0.62	0.256
WBC, 10^9/L, median (IQR)	9.88 (8.24)	8.75 (8.79)	10.1 (8.01)	0.132
Lymphocyte, 10^9/L, median (IQR)	0.67 (0.52)	0.74 (0.55)	0.66 (0.53)	0.748
Neutrophil, 10^9/L, median (IQR)	8.68 (7.98)	7.67 (8.17)	9.06 (7.88)	0.085
Hemoglobin, g/dL, mean±SD	11.87±2.67	12.1±2.49	11.81±2.72	0.702
Platelet, 10^9/L, mean±SD	231±135	228±112	232±141	0.559
Albumin, g/dL, mean±SD	3.42±0.8	3.53±0.65	3.4±0.83	0.644
LDH, u/L, median (IQR)	456 (286)	500 (362)	444 (236)	0.020
Creatinine, mg/dL, median (IQR)	1.28 (1.08)	0.94 (0.79)	1.35 (1.16)	<0.001
eGFR, median (IQR)	43.78 (43)	49.96 (44)	41.05 (43)	0.157
Troponin, ng/mL, median (IQR)	0.068 (0.207)	0.036 (0.145)	0.076 (0.218)	0.055
CK-MB, u/L, median (IQR)	21.1 (15.76)	19.3 (12.8)	21.58 (15.85)	0.126

CONCLUSION

This study described the comorbidities, laboratory parameters, and duration of hospitalization of young and elderly patients who died due to COVID-19. In the light of the study data, there was no significant intergroup difference. Further research is required on these parameters.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 18.11.2021, Decision No: 2021/719).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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REFERENCES

1. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579: 265-9.
2. Mohamadian M, Chiti H, Shoghli A, Biglari S, Parsamanesh N, Esmaeilzadeh A. COVID-19: Virology, biology and novel laboratory diagnosis. J Gene Med 2021; 23: e3303.
3. Abduljali J, Abduljali B. Epidemiology, genome and clinical features of the pandemic SARS-CoV-2: a recent view. New Micr New Infect 2020; 35: 100672.
4. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 deceased patients with COVID-19. J Med Virol 2020; 92: 2511-5.
5. Grygiel-Górniak B, Oduah MT. COVID-19: what should the general practitioner know? Clin Interv Aging 2021; 16: 43-56
6. Carpenter CR, Mudd PA, West CP, Wilber E, Wilber ST. Diagnosing COVID-19 in the emergency department: a scoping review of clinical examinations, laboratory tests, imaging accuracy, and biases. Acad Emerg Med 2020; 27: 653-70
7. Li Y, Ji D, Cai W, et al. Clinical characteristics, cause analysis and infectivity of COVID-19 nucleic acid repositive patients: a literature review. J Med Virol 2021; 93: 1288-95.
8. Nachtigall I, Lenga P, Jóźwiak K, et al. Clinical course and factors associated with outcomes among 1904 patients hospitalized with COVID-19 in Germany: an observational study. Clin Microbiol Infect 2020; 26: 1663-9.
9. Tan X, Zhang S, Xu J, et al. Comparison of clinical characteristics among younger and elderly deceased patients with COVID-19: a retrospective study. Aging (Albany NY) 2020; 13: 16-26.
10. Sawalha K, Abozenah M, Kadado AJ, et al. Systematic review of COVID-19 related myocarditis: insights on management and outcome. cardiovasc revasc Med 2021; 23: 107-13.
11. Arslan K, Baş S. Frequency of troponin elevations in patients with COVID-19 and clinical course in these patients. Anatolian Curr Med J 2022; 4: 95-102.
12. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. Eur J Epidemiol 2020; 35: 1123-38.
13. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. Eur J Epidemiol 2020; 35: 1123-38
14. Manivannan M, Jogalekar MP, Kavitha MS, Maran BAV, Gangadaran P. A mini-review on the effects of COVID-19 on younger individuals. Exp Biol Med (Maywood) 2021; 246: 293-7.
15. Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. Aging Male 2020; 23: 1416-24.
16. Garibaldi BT, Fiksel J, Muschelli J, et al. Patient trajectories among persons hospitalized for COVID-19: a cohort study. Ann Intern Med 2021; 174: 33-41
17. Şahin Özdemirel T, Akkurt ES, Ertan Ö, Gökler ME, Akıncı Özyürek B. Complications with moderate-to-severe COVID-19 during hospital admissions in patients with pneumonia. J Health Sci Med 2021; 4: 766-771.
18. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis 2020; 95: 304-7.
19. Assandri R, Buscarini E, Canetta C, Scartabellati A, Viganò G, Montanelli A. Laboratory biomarkers predicting COVID-19 severity in the emergency room. Arch Med Res 2020; 51: 598-9.
20. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol 2020; 11: 1446.
21. Al-Omari A, Alhuqbani WN, Zaidi ARZ, et al. Clinical characteristics of non-intensive care unit COVID-19 patients in Saudi Arabia: A descriptive cross-sectional study. J Infect Public Health 2020; 13: 1639-44.

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Relationship of the CRP/albumin ratio and the systemic immune-inflammation index with Forrest classification in patients with gastrointestinal bleeding

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ABSTRACT

Aim: The present study aimed to investigate CRP/albumin ratio and the systemic immune-inflammation index (SII) and Forrest classification in patients who presented to the emergency department with acute upper gastrointestinal (GI) bleeding.

Materials and Method: Patients over 18 years of age who presented to the emergency department of our hospital with melena, hematemesis, and hematochezia and were diagnosed with upper GI bleeding via esophagoduodenoscopy were included in the study. Esophagoduodenoscopy results, and accordingly, the Forrest classifications, together with complete blood count, including hemoglobin, platelet, and neutrophil values, as well as demographic characteristics were recorded. SII (calculated by multiplying the platelet count with neutrophil count and dividing the value obtained by the lymphocyte count [platelet (P)×neutrophil (N)/lymphocyte (L)]) and CRP/albumin ratio was calculated.

Results: No statistically significant difference was observed among the Forrest classification groups in terms of the median SII values as well as median CRP/albumin ratios. However, a statistically significant difference in median CRP/albumin ratios was observed among the dichotomized Forrest classification groups.

Conclusion: The SII is not a reliable parameter either predicts GI bleeding or the Forrest classification in patients with upper GI bleeding. The CRP/albumin ratio might be a poor predictor of bleeding; however, it can not predict the Forrest classification.

Keywords: CRP albumin ratio, Forrest classification, systemic immune-inflammation index, upper gastrointestinal bleeding

INTRODUCTION

Patients diagnosed with upper gastrointestinal (GI) bleeding are commonly present with various etiologies and symptoms. (1) Melena or hematemesis are common symptoms of upper GI bleeding at presentation. In rare cases, the symptoms also include hematochezia. Esophagoduodenoscopy is a useful diagnostic as well as a therapeutic procedure for patients with upper GI bleeding. (2) The Forrest classification is used during esophagoduodenoscopy to determine the severity of the symptoms and to indicate the risk of re-bleeding. The Forrest classification is as follows: Forrest Ia (Active Bleeding), Ib (Oozing Bleeding), IIa (Non-bleeding visible vessel), IIb (Glutinous clot), IIc (Flat spot), and III (Flat spot, clean base) (3).

The C-reactive protein (CRP)/albumin ratio is a new generation indicator of inflammation, and its usefulness has been shown in various types of cancer and sepsis. It has also been proven that this ratio can be used in traumatic brain injury. (4) Similar to the C-reactive protein (CRP)/albumin ratio, the Systemic Immune-Inflammation Index (SII) is a valuable prognostic parameter that can be obtained through routine blood tests and provides information about the inflammatory status of the patient in a number of medical conditions, including hepatocellular, colorectal, and pancreatic cancers. (5) It was determined that the CRP value showed 30-day mortality in non-variceal GI bleeding. (6) Also, studies have also been shown that CRP/albumin ratio is a prognostic marker for gastric cancer type. (7)

In a meta-analysis investigating the relationship between gastric cancers and SII value, it showed the relationship of SII value with tumor invasion and prognosis. (8) To the best of our knowledge, our study is the first to examine the CRP/albumin ratio and the relationship between SII and GI bleeding.

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The present study aimed to investigate these inflammatory indexes and Forrest classification in patients who presented to the emergency department with acute upper GI bleeding.

MATERIALS AND METHOD

The study was initiated with the approval of the Karabük University Hospital Non-interventional Clinical Research Ethics Committee (Date: 01.10.2021, Decision No: 2021/656). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

The present study was designed as a retrospective cross-sectional study. The patients over 18 years of age presented to the emergency department of our hospital between 09/01/2020 and 09/01/2021 with melena, hematemesis, and hematochezia and were diagnosed with upper GI bleeding via esophagoduodenoscopy. The study data were retrieved from the hospital information-processing system. Esophagoduodenoscopy results, and accordingly, the Forrest classifications, together with complete blood count, including hemoglobin, platelet, and neutrophil values, as well as demographic characteristics, such as age, and gender were recorded. The blood tests were performed during the first presentation to the emergency department. SII (calculated by multiplying the platelet count with neutrophil count and dividing the value obtained by the lymphocyte count [platelet (P)×neutrophil (N)/lymphocyte (L)]) and CRP/albumin ratio were calculated. Patients aged below 18 years; pregnant patients; patients with a history of hematological or autoimmune disease; those who recently underwent chemotherapy, radiotherapy, or blood transfusions; and those with lack of access to required data were excluded from the study.

Statistical Analysis

Statistical Package for the Social Sciences for Windows (IBM Corp., Armonk, NY, USA) was used for the statistical analyses of data. The normality of the distribution of continuous data was tested with the Shapiro–Wilk test and a histogram. Continuous normally distributed data were expressed in mean±standard deviation, and continuous non-normally distributed data were expressed in median (25%–75% quartile), whereas categorical data were expressed in frequency and percentage. Non-normally distributed continuous data was analyzed using the Mann–Whitney U test for paired group comparisons and Kruskal–Wallis test for multiple group comparisons. The Forrest classification was dichotomized into class 3 and others. The usefulness of the CRP/albumin ratio in predicting the dichotomized Forrest classification was analyzed using the Receiver Operating Characteristic (ROC) curve, and the criteria for the value of the CRP/albumin ratio based diagnostic test were calculated.

RESULTS

A total of 180 patients were included in the study; of these, patients who did not undergo esophagoduodenoscopy (n=29), those who underwent esophagoduodenoscopy for different purposes (such as peg insertion and foreign body removal) (n=21), and those with esophageal hemorrhages outside the Forrest classification (n=17) were excluded. 113 patients were included in the study. The median age was 64 years (45–75.5), and 82 (72.6%) of the patients were males. The basic descriptive characteristics of the study group are summarized in **Table 1**.

Table 1. Main descriptive characteristics of patients

Age (median [IQR])	64 (45–75.5)
Gender (Male) n (%)	82 (72.6)
Hemoglobin (g/dl) (mean±SD)	9.9 (2.9)
Neutrophil (10^3/uL) (median [IQR])	7 (5.5–9)
Lymphocyte (10^3/uL) (median [IQR])	1.8 (0.9–2.5)
Platelet (10^3/uL) (median [IQR])	218 (171.3–290.8)
Creatinine (mg/dl) (median [IQR])	0.9 (0.6–1.1)
INR (median [IQR])	1.12 (1.04–1.19)
CRP (mg/L) (median [IQR])	6.9 (1.8–47.6)
Albumin (g/dL) (median [IQR])	35.1 (29.2–37.7)
SII (median [IQR])	815.8 (542.4–1703)
CRP/Albumin Ratio (median [IQR])	0.21 (0.05–1.4)
Neutrophil/Lymphocyte Ratio (median [IQR])	3.7 (2.4–7.7)
Platelet/Lymphocyte Ratio (median [IQR])	126.1 (86.4–216.3)
Forrest Classification n (%)	113 (100)
Forrest 1a n (%)	1 (0.9)
Forrest 1b n (%)	13 (11.5)
Forrest 2a n (%)	4 (3.5)
Forrest 2b n (%)	9 (8)
Forrest 2c n (%)	15 (13.3)
Forrest 3 n (%)	71 (62.8)

CRP: C-reactive Protein, INR: International Normalized Ratio, SII: Systemic Immune-Inflammatory Index, SD: Standard Deviation,

No statistically significant difference was observed among the Forrest classification groups in terms of SII median values (p=0.655, Kruskal–Wallis). The Forrest classification was dichotomized into class 3 without bleeding and other classes with bleeding (**Table 2**). The difference in terms of SII median values among the groups with and without bleeding showed that there was no statistically significant difference among the groups (p=0.910, Mann–Whitney U).

Table 2*. Difference in the median Systemic Immune-Inflammatory Index (SII) values among the Forrest classification groups

	Forrest 1b	Forrest 2a	Forrest 2b	Forrest 2c	Forrest 3	p value**
SII (median (25%–75% quartile))	786.4 (478.4–2624)	813.6 (299.1–1293.4)	821.2 (714.2–2463.8)	660.8 (515.6–1235.3)	784.5 (540.3–1453)	0.655

* As there was only 1 patient in the Forrest 1a group, it could not be included in the analysis. ** Kruskal–Wallis test was used. P-values provided in boldface are statistically significant (p<0.05). SII: Systemic Immune-Inflammatory Index.

Table 3*. Difference in median Neutrophil–Lymphocyte Ratio (NLR), Platelet–Lymphocyte Ratio (PLR), and C-reactive Protein (CRP)/Albumin ratios among the Forrest classification groups

	Forrest 1b	Forrest 2a	Forrest 2b	Forrest 2c	Forrest 3	p value**
NLR (median [IQR])	7.1 (2.1–10)	3 (1.7–5.2)	3.7 (2.9–8)	3.7 (2.3–7.4)	3.4 (2.3–6.6)	0.862
PLR (median [IQR])	115.5 (87.7–231.4)	105.7 (50.4–135.6)	116.5 (98.3–267.7)	132.3 (90–207.6)	143.6 (84.7–219.6)	0.520
CRP/Albumin (median [IQR])	0.05 (0.02–0.49)	0.84 (0.7–4.7)	0.07 (0.02–0.57)	0.05 (0.04–3.70)	0.39 (0.08–2.52)	0.147

* As there was only 1 patient in the Forrest 1a group, it could not be included in the analysis. ** Kruskal–Wallis test was used. P-values in boldface are statistically significant (p<0.05). NLR: Neutrophil–Lymphocyte Ratio, PLR: Platelet–Lymphocyte Ratio, CRP: C-reactive Protein

No statistically significant difference was found in median CRP/albumin ratios among the Forrest classification groups (p=0.147, Kruskal–Wallis) (**Table 3**). However, the difference in the median CRP/albumin ratios among the dichotomized Forrest classification groups was statistically significant (p=0.023, Mann–Whitney U) (**Table 4**). While testing the diagnostic performance of the CRP/albumin ratio in predicting the presence of bleeding via endoscopy (Forrest 1a, 1b, 2a, 2b, and 2c) using ROC analysis, the area under the curve (AUC) was determined as 0.641 (**Figure 1**). The highest sum of sensitivity and specificity, i.e., 0.06, was set as the threshold value. According to the this threshold, the sensitivity of the test was 51.4% (95% confidence interval (CI): 34%–68.6%), specificity was 81% (95% CI: 68.6%–90.1%), positive likelihood ratio was 2.71 (95% CI: 1.46–5.05), negative likelihood ratio was 0.6 (95% CI: 0.42–0.86), positive predictive value was 62.1% (95% CI: 46.8%–75.3%), negative predictive value was 73.4% (95.8%–80%), and accuracy was 69.9% (95% CI: 59.5%–79%) (**Table 5**).

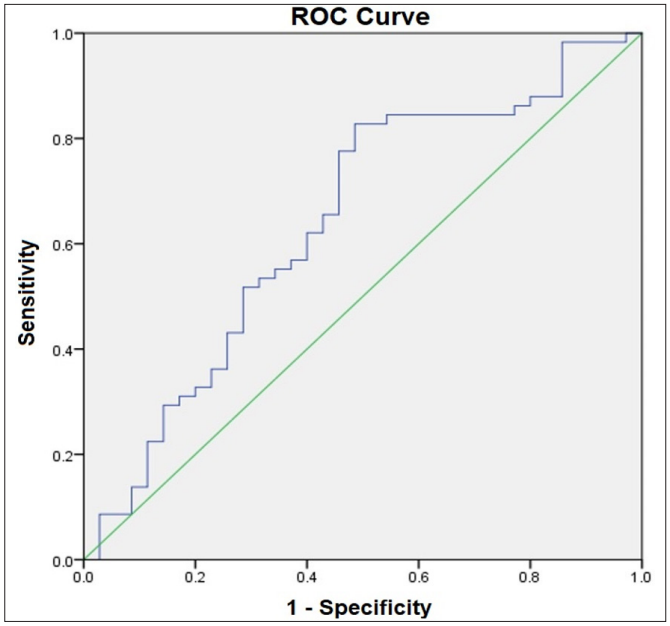

Figure 1. Receiver Operating Characteristic curve

Table 4*. Difference in median NLR, PLR, and CRP/Albumin ratios among the dichotomized Forrest classification groups

	Forrest 3	Forrest 1a, 1b, 2a, 2b, and 2c	p value**
NLR (median [IQR])	3.4 (2.3–6.6)	3.7 (2.3–8)	0.483
PLR (median [IQR])	143.6 (84.7–219.6)	116 (89.1–191.6)	0.695
CRP/Albumin (median [IQR])	0.39 (0.76–2.52)	0.05 (0.03–0.79)	0.023

* The Forrest classification was dichotomized into class 3 without bleeding and other classes with bleeding. ** Mann–Whitney U test was used. P-values provided in boldface are statistically significant (p<0,05). NLR: Neutrophil–Lymphocyte Ratio, PLR: Platelet–Lymphocyte Ratio, CRP: C-reactive Protein

Table 5. Diagnostic performance criteria of the CRP/Albumin ratio in predicting the presence of bleeding

AUC	0.641 (95% CI: 0.522–0.761)
Sensitivity	51.4% (95% CI: 34%–68.6%)
Specificity	81% (95% CI: 68.6%–90.1%)
Positive likelihood ratio	2.71 (95% CI: 1.46–5.05)
Negative likelihood ratio	0.6 (95% CI: 0.42–0.86)
Positive predictive value	62.1% (95% CI: 46.8%–75.3%)
Negative predictive value	73.4% (95% CI: 65.8%–80%)
Accuracy	69.9% (95% CI: 59.5%–79%)

AUC: Area Under the Curve, 95% CI: 95% Confidence Interval.

No statistically significant difference was observed among the Forrest classification groups in terms of the median neutrophil-lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) (p=0.862, p=0.520, Kruskal–Wallis, respectively). Moreover, there was no statistically significant difference among the dichotomized Forrest groups in terms of median NLR and median PLR (p=0.483, p=0.695, respectively, Mann–Whitney U). These results are summarized in **Tables 3** and **4**.

DISCUSSION

The SII is a new marker that is calculated using a complete blood count test and was shown to have been associated with adverse outcomes of cancer types.(9) It was first developed in 2014. (5) The SII reflects the balance between inflammatory status at the systemic

level. This index was comprehensively studied in recent years as it is inexpensive, easy to calculate, and easy to obtain. (9) The SII was reported to be a powerful predictor of poor prognosis and mortality in cardiovascular diseases, including endocarditis and pulmonary embolism, as well as a predictor of prognosis in patients with, for instance, kidney, lung, and prostate cancers. The SII was also used as a prognostic marker in patients with contrast-induced nephropathy, ischemic stroke, Bell's palsy, sinus vein thrombosis, intracerebral hemorrhage, glioma, and subarachnoid hemorrhage. (9-12) In a study conducted in patients with the acute coronary syndrome, they investigated the comorbidities of the patients using the Elixhauser Comorbidity Index and it was found that the SII value was higher in patients with comorbidity.(13) To the best of our knowledge, the usefulness of the SII was evaluated for the first time for upper GI bleeding in the present study; however, it was not a useful parameter in predicting the Forrest classification as well as in determining the likelihood of bleeding present during esophagoduednoendoscopy.

Several blood-related parameters, including CRP and albumin, are reported as prognostic markers for various diseases. (14-16) However, a single blood parameter is not to be reliable because such parameters are inevitably susceptible to a series of other diseases. (16) An elevated CRP alone often suggests an infective or inflammatory condition. (17) Elevated CRP was shown in relation to increased severity in various diseases, including ischemic heart disease, and chronic liver disease. (18,19) Higher serum CRP levels are associated with poor prognosis and increased mortality in patients with upper GI bleeding, (18-21) whereas low albumin levels are often associated with chronic diseases due to nutritional deficiencies. These parameters are easily accessible and often obtained automatically as a part of the application profile. (17) The CRP/albumin ratio is both a nutritional and inflammation-based index similar to the SII; thus, the same may increase in many diseases. (16) This ratio is less affected by age, despite the fact that prognosis in many diseases is affected by age. (17) The present study found that the CRP/albumin ratio might serve as a useful parameter in detecting upper GI bleeding upon dichotomization by the presence or absence of bleeding, but CRP/albumin ratio could not predict the Forrest classification. Based on the threshold value of 0.06, i.e., the highest sum of sensitivity and specificity, the sensitivity and the specificity of the test were 51.4% and 81%, respectively. Although it is not an ideal test in the given circumstances, its low cost and frequent request may favor its use.

NLR and PLR markers can be obtained and were shown to have been associated with negative outcomes in various types of cancers as well as inflammatory diseases and coronary artery-related diseases. (9) In the present study, it proved to be inadequate to predict either the Forrest classification or the presence of bleeding.

The median age of the 113 patients included in our study was 64 years; this is similar to the findings of many studies in the literature. (22-26) Diseases with a higher prevalence in older individuals and increased drug use associated with such diseases may account for the increased upper GI bleeding observed in older individuals. However, such data were not collected in the present study. A total of 72.6% of the patients in the present study were males. Except for a study by Okutur et al. (27), different rates in terms of sex were found in other studies. (22,23)

Limitations

It was a single-center study. There was no data regarding the prognosis of the patients, this study did not include the mortality and morbidity rates of the patients. Further prospective studies with larger numbers of patients are needed.

CONCLUSION

The SII is not a reliable parameter either predicts GI bleeding or the Forrest classification in patients with upper GI bleeding. The CRP/albumin ratio might be a poor predictor of bleeding; however, it can not predict the Forrest classification.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Karabük University Hospital Non-interventional Clinical Research Ethics Committee (Date: 01.10.2021, Decision No: 2021/656).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Kamboj AK, Hoversten P, Leggett CL. Upper gastrointestinal bleeding: etiologies and management. Mayo Clin Proc 2019; 94: 697-703.
2. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012; 107: 345-60.

3. Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. Lancet 1974; 17: 394-7.
4. Wang R, He M, Ou X, Xie X, Kang Y. CRP Albumin ratio is positively associated with poor outcomes in patients with traumatic brain injury. Clin Neurol Neurosurg 2020; 195: 106051.
5. Fest J, Ruiter R, Mulder M, et al. The systemic immune-inflammation index is associated with an increased risk of incident cancer-A population-based cohort study. Int J Cancer 2020; 1: 692-8.
6. Park SH, Mun YG, Lim CH, Cho YK, Park JM. C-reactive protein for simple prediction of mortality in patients with acute non-variceal upper gastrointestinal bleeding: a retrospective analysis. Medicine (Baltimore) 2020; 99: e23689.
7. Kudou K, Saeki H, Nakashima Y, et al. C-reactive protein/albumin ratio is a poor prognostic factor of esophagogastric junction and upper gastric cancer. J Gastroenterol Hepatol 2019; 34: 355-63.
8. Cao X, Xue J, Yang H, Han X, Zu G. Association of clinical parameters and prognosis with the pretreatment systemic immune-inflammation index (SII) in patients with gastric cancer. J Coll Physicians Surg Pak 2021; 31: 83-8.
9. Erdoğan M, Erdöl MA, Öztürk S, Durmaz T. Systemic immune-inflammation index is a novel marker to predict functionally significant coronary artery stenosis. Biomark Med 2020; 14: 1553-61.
10. Li C, Tian W, Zhao F, et al. Systemic immune-inflammation index, SII, for prognosis of elderly patients with newly diagnosed tumors. Oncotarget 2018; 19: 35293-9.
11. Gok M, Kurtul A. A novel marker for predicting severity of acute pulmonary embolism: systemic immune-inflammation index. Scand Cardiovasc J 2021; 55: 91-6.
12. Bağcı A, Aksoy F, Baş HA. Systemic immune-inflammation index may predict the development of contrast-induced nephropathy in patients with ST-segment elevation myocardial infarction. Angiology 2021; 12: 33197211030053.
13. Su G, Zhang Y, Xiao R, Zhang T, Gong B. Systemic immune-inflammation index as a promising predictor of mortality in patients with acute coronary syndrome: a real-world study. J Int Med Res 2021; 49: 3000605211016274.
14. Wu Z, Zhang J, Cai Y, et al. Reduction of circulating lymphocyte count is a predictor of good tumor response after neoadjuvant treatment for rectal cancer. Medicine (Baltimore) 2018; 97: e11435
15. Chen Z, Shao Y, Wang K, et al. Prognostic role of pretreatment serum albumin in renal cell carcinoma: a systematic review and meta-analysis. Onco Targets Ther 2016; 28: 6701-10.
16. Zhang Y, Xiao G, Wang R. Clinical significance of systemic immune-inflammation index (SII) and C-reactive protein-to-albumin ratio (CAR) in patients with esophageal cancer: a meta-analysis. Cancer Manag Res 2019; 7: 4185-200.
17. Fairclough E, Cairns E, Hamilton J, Kelly C. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. Clin Med (Lond) 2009; 9: 30-3.
18. Park SH, Mun YG, Lim CH, Cho YK, Park JM. C-reactive protein for simple prediction of mortality in patients with acute non-variceal upper gastrointestinal bleeding: a retrospective analysis. Medicine (Baltimore) 2020; 18: e23689.
19. Kaptoge S, Di Angelantonio E, Lowe G, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010; 9: 132-40.
20. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000; 35: 469-76.
21. Ho KM, Lee KY, Dobb GJ, Webb SA. C-reactive protein concentration as a predictor of in-hospital mortality after ICU discharge: a prospective cohort study. Intensive Care Med 2008; 34: 481-7.
22. Yalçın M, Kara B, Öztürk NA, Ölmez Ş, Taşdoğan BE, Taş A. Epidemiology and endoscopic findings of the patients suffering from upper gastrointestinal system bleeding. Dicle Tıp Derg 2016; 43: 73-6.
23. Kandiş H, Korkut S, Korkut E. Akut üst gastrointestinal kanamalı olgularımızın endoskopik sonuçları. Duzce Med J 2010; 12: 17-20.
24. Özen E, Tekin F, Oruç N, et al. Varis dışı üst gastrointestinal sistem kanamalı 412 olgunun irdelenmesi. Akademik Gastroenteroloji Derg 2007; 6: 62-7.
25. Alper E, Baydar B, Çekiç C, Aslan F, Akça S, Ünsal B. Varise bağlı olmayan üst gastrointestinal sistem kanamasında endoskopik bulgular ve kanamayla ilişkileri. Endoskopi Gastrointestinal 2010; 18: 27-31.
26. Gölgeli H, Ecirli Ş, Kutlu O, Başer H, Karasoy D. Üst gastrointestinal sistem kanaması nedeniyle izlenen hastaların değerlendirilmesi. Dicle Tıp Derg 2014; 41: 495-501.
27. Okutur SK, Alkım C, Bes C, et al. Akut üst gastrointestinal sistem kanamaları: 230 olgunun analizi. Akademik Gastroenteroloji Derg 2007; 6: 30-6.

Original Article

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The use of predialysis glucose as long term glycemic marker in hemodialysis patients

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ABSTRACT

Aim: The major cause of chronic renal disease (CRD) is diabetes mellitus (DM). Although there are some other long term glycemic markers available, HbA1c remains the gold standart in CRD. In this study we aimed to explore the relation between average predialysis glucose and HbA1c levels.

Material and Method: 101 diabetic hemodialysis patients from two centers were included in this study. Last 2 and 3 months' average predialysis glucose levels were obtained. After 3 months, HbA1c levels were also studied.

Results: A significant and strong correlation between HbA1c and both 2 and 3 months' average predialysis glucose levels were found ($p<0.001$ and $R=0.700$, $p<0.001$ and $R=0.727$, The average of last 2 and respectively). Median of estimated glucose levels [146 (85-269) mg/dl] was lower than both median average of 3 months' predialysis glucose [172.6 (80-396) mg/dl] and median average of 2 months' predialysis glucose [180.5 (73-407) mg/dl] levels. Hb levels were not statistically different after grouping for HbA1c ≥7% and HbA1c <7%.

Conclusion: 3 months' predialysis glucose levels are strongly correlated with HbA1c levels. Although there are long term glycemic markers available, average predialysis glucose is an easy, cheap and reachable method for glycemic control.

Keywords: Predialysis glucose, HbA1c, long term glycemic marker, chronic renal disease, hemodialysis

INTRODUCTION

Chronic renal disease (CRD) is frequent in general population. 8-18% of adult population are estimated to have CRD (1). The major cause of CRD is diabetes mellitus (DM) and 20-40% of patients with DM developes CRD (2,3). 30-50% of end stage renal disease is considered to be secondary to DM (4). Glycemic control is crucial, for it predicts the morbidity and mortality of patients with diabetic renal disease (5). Glycated hemoglobin, known as hemoglobin A1c (HbA1c), is the most commonly used long term glycemic marker, which reflects the mean blood glucose during the preceeding 8-12 weeks (6). HbA1c is used for decades to assess the glycemic control in diabetic patients as a gold standard (7). Though, some limitations seems to affect the usage of HbA1c in individuals with CRD. Anemia, which is frequent in CRD, may alter HbA1c values. Anemia is mainly due to inadequate production of erythropoietin in CRD. Erythropoietin deficiency along with or without iron and vitamin B12 deficiency lead to increased circulating aged red blood cells, resulting in increased HbA1c levels due to long term exposure of glucose (8,9). Besides, acidosis due to CRD results in increased glycation (10). On the other hand, anemia treatment with iron and erythropoiesis stimulating agents leads to circulating immature red blood cells, which in turn causes decreased levels of HbA1c values (11). Although continuous glucose monitoring (CGM) as well as some other biomarkers of long term glycemic control like fructosamine (FA), glycated albumin (GA) and 1,5-anhydroglucitol (1,5-AG) are available, HbA1c is still widely used because of its low cost, best studied nature and availibility at all around the world. Indeed, Kidney Disease Improving Global Outcome (KDIGO) and American Diabetes Association (ADA) guidelines are recommending to use HbA1c for long term glycemic control (12,13). Despite the well documented relationship between fasting plasma glucose and HbA1c values in non-CRD diabetic individuals, it seems to be altered as renal disease progresses (14).

In this study we aimed to explore the relation between predialysis glucose and HbA1c values in hemodialysis patients.

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MATERIAL AND METHOD

This study was approved by KTO Karatay University Faculty of Medicine, Non-Pharmaceutical and Medical Device Researchs Ethics Committee Presidency (Date: 08.06.2021, Decision No: E-41901325-050.99-10015-006). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was performed in two hemodialysis center. 101 diabetic patients who were on hemodialysis at least for 3 months were included in this study. Patients who were under 18 years old, who undergone major surgery, who had active hemorrhage or had blood transfusion in last 3 months were excluded. Patient characteristics like age, gender, dialysis vintage were noted. Weight and height of every patient were obtained to calculate body mass index as kg/m2. Serum glucose, creatinine, blood urea nitrogen, calcium, phosphorus, potassium, sodium, albumin, C-reactive protein (CRP), parathormone (PTH), ferritin, bicarbonate, uric acid, triglyceride (TG), cholesterol and complete blood cell count samples were obtained predialysis and were measured using automated and standardized methods. Serum glucose levels were obtained from routine monthly laboratory tests as spot glucose which was not related with previous meal. Last 3 months' serum glucose levels were used to calculate last 3 and 2 months' average predialysis glucose. HbA1c was measured at the end of 3 months. Glucose measurements were done by Roche COBAS 8000 c 702 module and HbA1c measurements by Arkray ADAMS HA-8180V system. Estimated average glucose was calculated by eAG= 28.7 x HbA1c- 46.7 formula (15).

The statistical analysis were done by SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA.) for Windows version 22. After Kolmogorow-Smirnov normality test, correlation was done by Pearson correlation for parametric and Spearman correlation for non-parametric variables. Mann-Whitney U test was performed for non-parametric variables. A p value of <0.05 was considered statistically significant.

RESULTS

101 diabetic hemodialysis patients with a mean age of 62.79±12.40 were studied. 51 (%50.50) were men. Patient characteristics are shown in **Table 1**. Median HbA1c was 6.7% (4.6-11.0), median of estimated glucose levels according to HbA1c was 146 (85-269) mg/dl, median average of 3 months' predialysis glucose was 172.6 (80-396) mg/dl, median average of 2 months' predialysis glucose was 180.5 (73-407) mg/dl and median BMI was 27.31 (14.67-41.72) kg/m2. 2 and 3 months' average predialysis glucose levels were significantly positively correlated with estimated glucose according to HbA1c (p=0.000, R=0.700 and p=0.000, R=0.727 respectively) (**Table 2**). 2 and 3 months' average glucose levels were significantly positively correlated (p=0.000, R=0.946). HbA1c levels were significantly positively correlated with BMI (p=0.025, R=0.222), CRP (p=0.016, R=0.240) and TG levels (p=0.047, R=0.198). There were no difference between gender and in terms of HbA1c, 2 and 3 months' average glucose levels. After grouping HbA1c for ≥7% and <7%, there were no difference in terms of Hb levels [11.5 (8.1-13.9) and 11.25 (8.1-14.4) respectively, p=0.445].

Table 1. Patient characterisitics

Parameter	Mean values
Age (years)	62.97±12.40
Dialysis vintage (months)	50.71±1.38
Body mass index (kg/m²)	27.46±5.49
Hemoglobin (g/dl)	11.17±1.38
Albumin (g/dl)	3.82±0.39
Ferritin (µg/l)	609.15±455.04
Calcium (mg/dl)	8.44±0.62
Phosphorus (mg/dl)	4.97±1.29
Parathormone (µg/l)	390.12±358.14
C reactive protein (mg/l)	13.00±19.41
Triglyceride (mg/dl)	194.11±113.93

Table 2. Correlation of predialysis glucose with HbA1c.

Parameters	p and R value of correlation
2 months' average glucose	p<0.0001, R=0.700
3 months' average glucose	p<0.0001, R=0.726

DISCUSSION

In this study, predialysis glucose levels were found to be significantly positively correlated with HbA1c in diabetic hemodialysis patients. Both 3 and 2 months' average predialysis glucose levels were compatible with HbA1c. Estimated glucose was found to be lower than measured average 2 and 3 months' average predialysis glucose levels.

There are new long term glycemic control markers. Especially CGM seems to be a promising method in dialysis population (16). But its cost and inavailibility limits the use of CGM. Although affected by many parameters, HbA1c is still widely used to monitor long term blood sugar control in diabetic hemodialysis patients.

Sayed et al. (17) obtained 54 spot capillary blood glucose readings during 3 months and they calculated the mean glucose value of each patient. They showed that measured and expected HbA1c were significantly different among hemodialysis patients with DM. However the number of participants was low, as only 45.

In an another study of George et al. (18), HbA1c levels were found to be significantly correlated with fasting

plasma glucose in stage 3-5 CRD patients. They claimed that the association between fasting glucose and HbA1c decreased as renal disease progressed. However, this study did not include hemodialysis patients or previously known diabetic patients.

Speeckaert et al. (11) reviewed different long term glycemic markers in dialysis patients with DM. HbA1c was compared with GA, FA, 1,5-AG and CGM. They recommended the use of HbA1c as long term glycemic marker in dialysis patients because of its availibility and the other long term markers were insufficient to prove superiority.

Similarly, in the review of Copur et al. (9), the use of CGM and HbA1c was found to be valid as long term glycemic control markers in CRD patients. The latter was more favoured because of its availibility and best studied nature.

In the meta-analysis of Wang et al. (19), the strength of CGM in diabetic patients on dialysis was investigated. They found a significant positive correlation between CGM and HbA1c.

Hayashi et al. (20) studied 97 hemodialysis patients with DM. They were enrolled to a 72 hours CGM. HbA1c and GA samples were obtained thereafter. They found a better relation between HbA1c and CGM, rather than GA. They also concluded that HbA1c were found to be underestimated comparing to average glucose levels.

Watanabe et al. (21), investigated the relation of serum glucose levels with HbA1c and GA on 71 peritoneal dialysis patients. They found that serum glucose levels of both diabetic and non-diabetic peritoneal dialysis patients were significantly correlated with HbA1c, but not correlated with GA.

CGM was done on 80 diabetic chronic kidney disease patients in the study of Presswala et al. (22). HbA1c was significantly correlated with continuous glucose monitoring. HbA1c was found to be a more reliable method compared to fructosamine in diabetic CRD patients.

In the glycemic indices in dialysis evaluation (GIDE) study, Williams et al. (23) investigated long term glycemic markers on 1758 diabetic end stage renal disease patients (1476 on hemodialysis, 282 on peritoneal dialysis). This was the largest study up to date exploring glycemic markers in diabetic dialysis population and showed a significant correlation of casual glucose and HbA1c levels ($p<0.0001$, $R=0.69$), both in diabetic hemodialysis and peritoneal dialysis patients. In this study HbA1c underestimated casual glucose levels. Our study is consistent with this study in terms of correlation of glucose with HbA1c levels and the underestimation of HbA1c.

The main limitation of our study is the relatively small sample size. We did not use fasting glucose because it is hard to obtain fasting especially in midday and evening diabetic hemodialysis groups. Similarly, in the large populated GIDE study casual glucose –defined as not related to last meal- was investigated along with other long term glycemic control markers. We also found that HbA1c underestimated average glucose levels, which is consistent with some other studies (20,23). This finding also may favour the use of predialysis glucose levels.

CONCLUSION

This study revealed that last 2 and 3 months' average predialysis glucose levels are strongly correlated with HbA1c in diabetic hemodialysis patients. Despite long term glycemic markers are available, average predialysis glucose is an easy, cheap, reliable and reachable method for glycemic control. This relation has to be confirmed by large populated studies.

ETHICAL DECLERATIONS

Ethics Committee Approval: This study was approved by KTO Karatay University Faculty of Medicine, Non-Pharmaceutical and Medical Device Research Ethics Committee Presidency (Date: 08.06.2021, Decision No: E-41901325-050.99-10015-006).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. PLoS One 2016; 11: e0158765.
2. Levey AS, Coresh J. Chronic kidney disease. Lancet 2012; 379: 165-80
3. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis 2014; 64: 510-33.
4. United States Renal Data System 2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2021.
5. Mehdi U, Toto RD. Anemia, diabetes, and chronic kidney disease. Diabetes Care 2009; 32: 1320-6.

6. Consensus Committee. Consensus statement on the worldwide standardization of the hemoglobin A1C measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Diabetes Care 2007; 30: 2399-400.
7. Gomez-Peralta F, Choudhary P, Cosson E, Irace C, Rami-Merhar B, Seibold A. Understanding the clinical implications of differences between GMI and HbA1c. Diabetes Obes Metab 2022. doi: 10.1111/dom.14638.
8. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A(1c) in the management of diabetes. J Diabetes 2009; 1: 9-17.
9. Copur S, Onal EM, Afsar B, et al. Diabetes mellitus in chronic kidney disease: Biomarkers beyond HbA1c to estimate glycemic control and diabetes-dependent morbidity and mortality. J Diabetes Complications 2020; 34: 107707
10. Selvaraj N, Bobby Z, Sridhar MG. Increased glycation of hemoglobin in chronic renal failure: [corrected] potential role of oxidative stress. Arch Med Res 2008; 39: 277-84.
11. Speeckaert M, Van Biesen W, Delanghe J, et al; European Renal Best Practice Guideline Development Group on Diabetes in Advanced CKD. Are there better alternatives than haemoglobin A1c to estimate glycaemic control in the chronic kidney disease population? Nephrol Dial Transplant 2014; 29: 2167-77.
12. American Diabetes Association Professional Practice Committee; , Draznin B, Aroda VR, Bakris G, et al. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. Diabetes Care 2022; 45: S83-S96.
13. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int 2020; 98: S1-S115.
14. Jung M, Warren B, Grams M, et al. Performance of non-traditional hyperglycemia biomarkers by chronic kidney disease status in older adults with diabetes: results from the atherosclerosis risk in communities study. J Diabetes 2018; 10: 276-85.
15. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008; 31: 1473-8.
16. Bomholt T, Adrian T, Nørgaard K, et al. The use of HbA1c, glycated albumin and continuous glucose monitoring to assess glucose control in the chronic kidney disease population including dialysis. Nephron 2021; 145: 14-9.
17. Sayed M, Adnan F, Majeed M. Is HbA1c a true marker of glycaemic control in diabetic patients on haemodialysis? J Ayub Med Coll Abbottabad 2019; 31: 46-50.
18. George C, Matsha TE, Korf M, Zemlin AE, Erasmus RT, Kengne AP. The agreement between fasting glucose and markers of chronic glycaemic exposure in individuals with and without chronic kidney disease: a cross-sectional study. BMC Nephrol 2020; 21: 32.
19. Wang F, Wang D, Lyu XL, Sun XM, Duan BH. Continuous glucose monitoring in diabetes patients with chronic kidney disease on dialysis: a meta-analysis. Minerva Endocrinol 2020 Dec 3.
20. Hayashi A, Takano K, Masaki T, Yoshino S, Ogawa A, Shichiri M. Distinct biomarker roles for HbA1c and glycated albumin in patients with type 2 diabetes on hemodialysis. J Diabetes Complications 2016; 30: 1494-9.
21. Watanabe Y, Ohno Y, Inoue T, Takane H, Okada H, Suzuki H. Blood glucose levels in peritoneal dialysis are better reflected by HbA1c than by glycated albumin. Adv Perit Dial 2014; 30: 75-82.
22. Presswala L, Hong S, Harris Y, et al. Continuous glucose monitoring and glycemic control in patients with type 2 diabetes mellitus and CKD. Kidney Med 2019; 1: 281-7.
23. Williams ME, Mittman N, Ma L, et al. The glycemic indices in dialysis evaluation (GIDE) study: comparative measures of glycemic control in diabetic dialysis patients. Hemodial Int 2015; 19: 562-71.

Original Article

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Platelet-lymphocyte ratio predicts poor prognosis in stage II / III colon and rectum cancer

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ABSTRACT

Objective: There is an increasing number of studies in the literature reporting that serum platelet/lymphocyte ratio (PLR) can provide useful prognostic data for various cancers. In the present study, the effects of platelet-lymphocyte ratio on survival in stage II/III colorectal cancers (CRC) were examined.

Material and Method:A total of 106 Stage II/III CRC patients who underwent curative surgery 2015-2020 were included in the study. Emergency cases and patients diagnosed with other than adenocarcinoma were excluded from the study. The demographic data of the patients, preoperative imaging and laboratory results, postoperative pathology reports, and patient follow-up examination data were obtained from hospital records. The relations between demographic, histopathological, hematological values and the prognosis was analyzed in terms of statistical significance.

Results:Among the 106 patients, 62 (58.5%) were male and 44 (41.5%) were female. The mean age was 64.3±12.01 (23-89). The mean follow-up period was calculated as 24.6±15.8 (2-63) months. When the pathology reports were reviewed, it was found that the mean tumor diameter was 5.3±2.33 cm (2-17) and the mean metastatic lymph node was 1.8±2.4 (0-10). The PLR ratio was determined as a poor prognostic factor affecting survival in the cox regression analysis, in which preoperative complete blood count, c-reactive protein and albumin values, neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and PLR were compared, and was separated from other variables (P=0.002 CI= 95%). When variables such as age, clinical stage, and tumor diameter were included in the model, PLR was similarly found to be an important predictive variable (P= 0.002). When only NLR, LMR, and PLR were evaluated, PLR again came to the forefront with a significance value of P=0.01. Also, high neutrophil count, increased platelet distribution volume (PDW), advanced age, and perineural invasion (PNI) were found to be significant factors in predicting poor prognosis.

Conclusions: High PLR is a poor prognostic factor for CRC patients. For this reason, it may be necessary to follow a more aggressive strategy in the management of postoperative treatment in patients who have high PLR.

Keywords: Platelet/Lymphocyte Ratio, adjuvant chemotherapy, colorectal cancer, Stage II/III, prognostic factor.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer on a global scale after lung cancer excluding gender-specific prostate and breast cancer. Stage II-III CRCs are the most common patient group in daily practice (1,2). In many previous studies, parameters such as biological characters such as tumor stage, histological grade, lympho-vascular invasion (LVI), peri-neural invasion (PNI), and the number of metastatic lymph nodes, obstruction, perforation, serum carcinoembryonic antigen (CEA) levels were defined as clinicopathological prognostic factors for CRC (3-7). Although these factors are guiding in the choice of treatment, there are still many uncertainties in terms of the treatment modality. Different biological features in tumors may cause resistance in treatment, and patients at the same stage may show different clinical outcomes (8,9). On the other hand, although the benefit of adjuvant chemotherapy in stage III CRC was demonstrated in many studies, it is still a matter of debate to which patient group it should be given in stage II CRC. For this reason, standardized and reliable prognostic biomarkers are needed to identify high-risk patients especially in stage II-III CRCs (10-13).

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It was shown in various studies that cells that are involved in inflammation play important roles in many stages such as carcinogenesis, tumor progression, invasion, and metastasis. It is considered that these cells, especially platelets, lymphocytes, neutrophils, and macrophages can provide useful data on the biological behaviors of the tumor by helping the traditional pathological staging classifications. These cells were used individually or in various combinationsin the literature (14,15).

It was documented that the lymphocytes in the tumor microenvironment can recognize abnormally expressed neoantigens, attack cancer cells, and play roles in regression. In previous studies, various factors such as platelet derived growth factor (PDGF), platelet factor-4, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and thrombospondin that are secreted from platelets are involved in the proliferation of tumor cells, growth of tumor mass, and metastasis. It was also reported that the platelet/lymphocyte ratio (PLR) is a poor prognostic factor in various cancers such as ovarian, breast, lung, and pancreas, and is associated with decreased survival rates (16-20).

However, there are some difficulties in making use of these parameters in the clinical practice. For example, there are many different opinions regarding the evaluation methods and cut-off values. There are also inconsistencies in the results because of the limited number of studies on combinations between inflammatory cells and heterogeneous patient groups. In the present study, the relations between preoperative serum platelet-lymphocyte ratio (PLR) and survival were investigated in stage II-III CRC patients who were given adjuvant chemotherapy after curative surgery.

MATERIAL AND METHOD

This study was approved by Tekirdağ Namık Kemal University Non-interventional Clinical Research Ethics Committee (Date: 25.01.2022, Decision No: 2022.05.01.05). The study was conducted in line with the ethical standards of the Institutional/National Research Committee and 1964 Helsinki Declaration.

Data Sources

The study was conducted in Tekirdağ Namık Kemal University, Department of General Surgery. The data of 230 patients who underwent curative surgery for CRC between 2015 and 2020 were analyzed retrospectively in the study. The demographic data of the patients, preoperative imaging and laboratory results, postoperative pathology reports, and patient follow-up examination data were obtained from the archives of Tekirdağ Namık Kemal University. A total of 106 patients who met the criteria were included in the study.

Patient Population

All 106 patients who had data integrity were patients with stage II-III colorectal adenocarcinoma, and each received systemic chemotherapy in the postoperative period. Exclusion criteria were listed as follows; patients who were operated on under emergency conditions, patients who underwent laparoscopic-robotic surgery, cases diagnosed other than adenocarcinoma, patients who died in the early postoperative period (in 1 month), cases who died because of reasons not related to the disease, stage I and stage IV patients, patients not receiving chemotherapy, and cases with chronic inflammatory comorbidities.

Hematological Examination

The blood samples collected preoperatively in standard tubes containing ethylenediaminetetraacetic acid (EDTA) were analyzed by using an automated hematology analyzer (BeckmanCoulter, CA, the USA) and evaluated by an experienced biochemist. The platelet (x103/μL), lymphocyte (x109/L), and other blood parameter counts, NLR, LMR, and PLR were calculated. Systemic inflammation score (SIS), modified glasgow prognostic score (mGPS), albumin-NLR score, and prognostic nutritional index (PNindex) scores are shown in **Table 1**.

Table 1. Prognostic scoring systems

SIS	0	LMR ≥3.8	and	Albumin ≥39.75 g/l
	1	LMR <3.8	or	Albumin <39.75 g/l
	2	LMR <3.8	and	Albumin <39.75 g/l
MGPS	0	CRP ≥10 mg/l		
	1	CRP <10 mg/l	and	Albumin ≥3.5 g/dl
	2	CRP <10 mg/l	and	Albumin <3.5 g/dl
Albumin-NLR	0	Albumin ≥39.75 g/l	and	NLR <2.39
	1	Albumin <39.75 g/l	or	NLR ≥2.39
	2	Albumin <39.75 g/l	and	NLR ≥2.39
PN index	10×Albumin g/dl + 0.005×Total Lymphocyte mm³			

SIS : SystemicInflammationScore, MGPS: Modified Glasgow PrognosticScore, PN index: PrognosticNutritionalIndex

Histopathologic Evaluation

The slides and paraffin blocks of the patients were evaluated again by an experienced pathologist by using a conventional light microscope (Nikon Eclipse E600, Nikon AG Instruments, Switzerland) and x10-x20 objective. The grade, presence of LVI, and presence of PNI were verified. The tumor sizes and metastatic lymph node ratios were scanned retrospectively.

Follow-up

Regarding the overall survival (OS), the time between the date of primary surgery and the date of disease-related death was calculated. The patients were contacted by using the contact numbers in the hospital records to determine these data. The patients were seen every 3 months for the first 2 years, every 6 months for the next 3 years, and then

annually. A complete physical examination was performed and tumor markers and biochemical tests were evaluated in the patient follow-up examinations. Control colonoscopy was performed 1 year after the surgery. If no pathological condition was detected, the second colonoscopy was performed 3 years later at the earliest. Chest flat film was performed every 3 months for the first 2 years. Abdominal computed tomography scans were performed every 6 months for the first 2 years. The patients were followed as of the date of surgery until February 2021 and the survival time was determined.

Statistical Evaluation

The Cox Regression Analyzes were performed to calculate the effects of the independent variables on survival. When survival groups were compared multivariately, a 95% Confidence Interval and a Hazard Ratio (HR) of 1.0 were used to identify the independent prognostic factors. The Log-Rank Test was used to compare the survival groups univariately, and survival curves were presented with the Kaplan-Meier Method. The area under the curve (AUC) was calculated by performing ROC analysis for significant laboratory values. The cut-off values were calculated based on the highest true positive and lowest false negative rates for the variables with AUC > 50%. The mean, range, standard deviation, and percentages were used to note the descriptive variables. The distributions of the independent variables were analyzed with the Shapiro-Wilk Test. The Pearson Correlation Tests were preferred for parametric data and the Spearman Correlation Tests were preferred for non-parametric data. The IBM SPSS statistics ver. 22 was used for all statistical analyses.

RESULTS

Among the 106 patients, 62 (58.5%) were male, and 44 (41.5%) were female. The mean age was 64.3±12.01 (23-89). The mean follow-up period was calculated to be 24.6±15.8 (2-63) months. When the pathology reports were reviewed, it was found that the mean tumor diameter was 5.3±2.33 cm (2-17) and the mean metastatic lymph node was 1.8±2.4 (0-10). It was determined at the end of the follow-up period that 81 patients, 25 of whom died, continued to survive. Tumor localizations and numbers were; cecum 9, ascending colon 13, hepatic flexure 6 (right colon 28), transverse colon 4, splenic flexure 5, descending colon 6, sigmoid colon 26, recto-sigmoid region 10, rectum 24, and synchronous tumor 3, respectively. As a result of the re-evaluation of paraffin blocks and slides, the presence of LVI was found in 69 patients and the presence of PNI in 36 patients. The number of Grade 1-2-3 tumors was 17, 83, and 6, respectively. When the pathological stages were classified, the number of stage 2A-2B-3A-3B and 3C patients were found to be 32, 10, 11, 34, and 19, respectively.

The demographic characteristics of the patients, biological characteristics of the tumor, preoperative blood count, serum albumin and CRP levels, NLR, LMR and PLR ratios,and mGPS, SIS, and albumin-NLR scores were evaluated by using the Backward Method in Cox Regression Analysis. PLR rate was separated from other variables as a poor prognostic factor affecting survival (P=0.002 CI= 95%). It was calculated that one-unit increase in PLR value increased the risk of death 1.028 times. In the Chi-Square Analysis, a PLR value of 197 and above was found to be linearly related to deaths (P=0.005). The variables that were found to be significant in predicting poor prognosis are shown in **Table 2**. The cut-off values of PLR, neutrophil, PDW, and age were found as; 197, 4.74, 19.75, and 72.5, respectively. The ROC Analysis and survival curves are shown in **Figure 1**. **Table 3** summarizes the relations between PLR and other variables.Among scoring systems such as albumin -NLR, SIS, mGPS, and PN index, albumin-NLR score (the worst prognosis =2, the best prognosis=0) was determined as the most important predictive factor (P=0.039).

Table 2. Significant factors predicting poor prognosis for OS

Variables	P Value	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Age	0.015	1.108	1.020	1.205
PNI	0.008	13.633	1.967	94.490
PDW	0.005	1.438	1.114	1.858
NEU	0.004	3.344	1.479	7.561
PLR	0.002	1.028	1.010	1.046

OS: Overall survival, Exp(B): Exponentiation of the B coefficient. PNI: Peri-neural invasion, PDW:Plateletdistributionwidth, NEU: Neutrophil, LYM: Lymphocyte, PLR: Platelet/Lymphocyte Ratio

Table 3. Association between PLR and other variables

Variables		PLR>197	PLR<197	P value
Gender	Female	15 (34.1%)	29 (65.9%)	0.84
	Male	20 (32.3%)	42 (67.7%)	
Age	<72.5	25 (30.9%)	56 (69.1%)	0.39
	>72.5	10 (40%)	15 (60%)	
Localization	Right	10 (35.7%)	18 (64.3%)	0.72
	Others	25 (32.1%)	53 (67.9%)	
T Stage	2-3	29 (31.2%)	64 (68.8%)	0.28
	4	6 (46.2%)	7 (53.8%)	
Grade	1	3 (17.6%)	14 (82.4%)	0.14
	2-3	32 (36%)	57 (64%)	
LVI	+	25 (36.2%)	44 (63.8%)	0.33
	-	10 (27%)	27 (73%)	
PNI	+	13 (36.1%)	23 (63.9%)	0.62
	-	22 (31.4%)	48 (68.6%)	
N Stage	0	15 (32.6%)	31 (67.4%)	0.59
	1	16 (37.2%)	27 (62.8%)	
	2	4 (23.5%)	13 (76.5%)	
Clinical Stage	2	9 (21.4%)	33 (78.6%)	0.04 (OR=2.50)
	3	26 (40.6%)	38 (59.4%)	
Survival	Ex	14 (56%)	11 (44%)	0.05(OR=3.63)
	Alive	21 (25.9%)	60 (74.1%)	

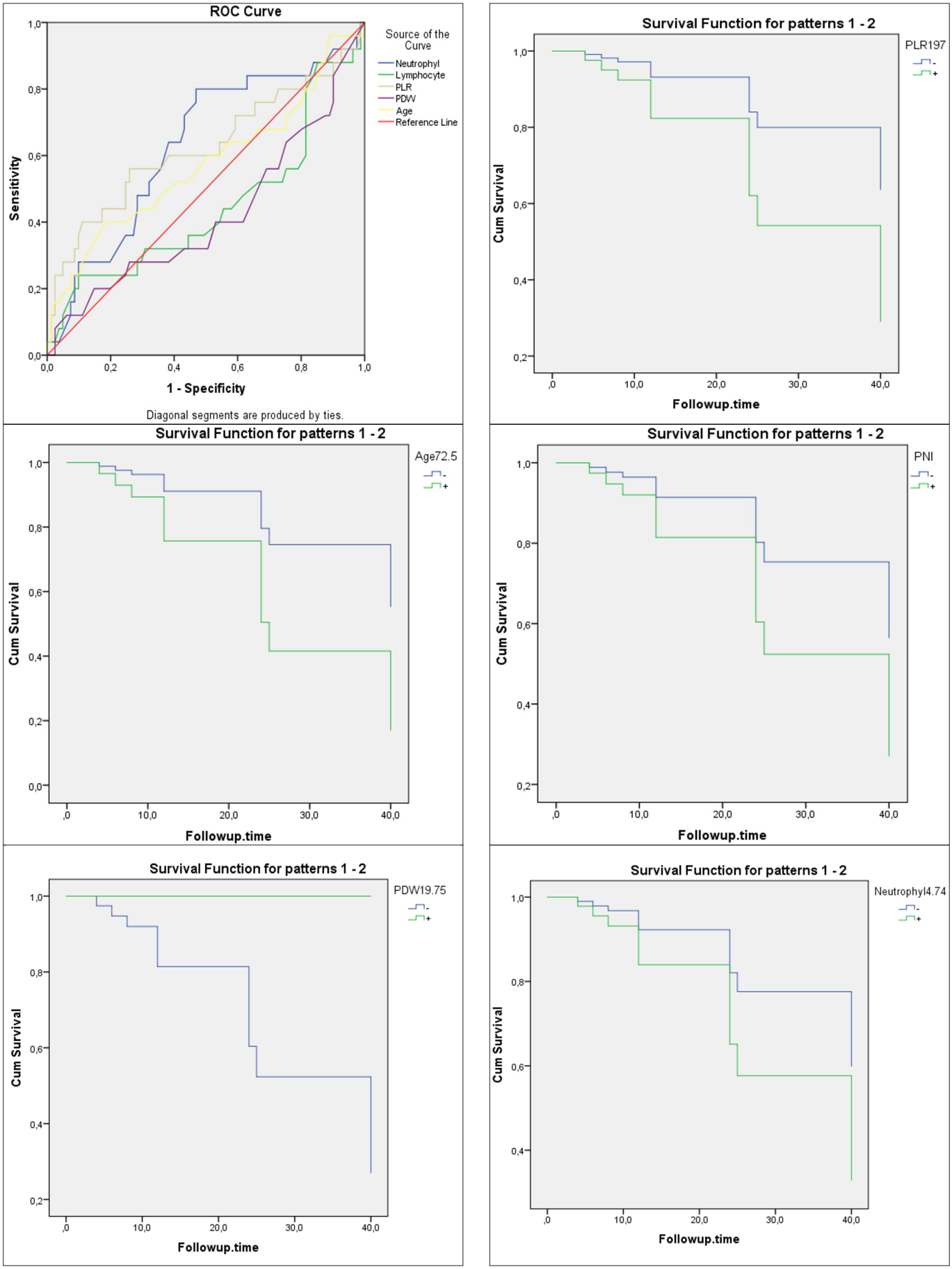

Figure 1. ROC analysisandsurvivalcurves of poorprognosticpredictors (for PLR: AUC=0.622 Cut-off: 197).

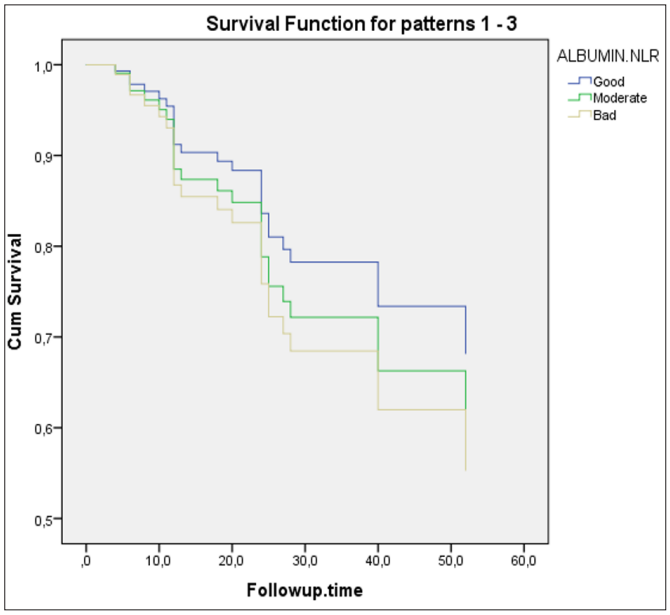

Figure 2. Albumin-NLR Survivalcurve

DISCUSSION

Many genetic and environmental risk factors play roles in the development of CRC (21). In the present study, it was shown that advanced age, high neutrophil count, PNI, high PDW, and high PLR were associated with poor prognosis and decreased survival.

The age is an important risk factor for CRC. The incidence begins to increase at significant levels after the age of 50; and 90% of CRC cases are seen after this age (22). The most common age group is the 6th and 7th decades. CRC is the most common type of cancer in individuals who are over 75 years of age in the USA with an incidence similar between men and women (23). In the present study, the incidence of CRC was found to be higher in elderly patients, in line with the literature data.

The relations between inflammation and cancer were first described by Rudolf Virchow in 1863. He detected the presence of neoplastic tissues and leukocytes in the regions where chronic inflammation occurred and observed that cancer cells developed from these regions. In their study, Balkwill and Mantovani (14, 15) reported that inflammation is an important factor for the development of solid tumor malignancies, and some solid organ malignancies can trigger an intrinsic inflammation to form the basis of the inflammatory microenvironment with pro-tumorigenic effects with a critical role in tumor resistance. De Visser et al. (24) showed that the tumor microenvironment includes macrophages, neutrophils, mast cells, natural killers, dendritic cells, T and B lymphocytes, fibroblasts, endothelial cells, pericytes, and mesenchymal cells in different types of inflammation. These different cells communicate with each other in different ways. As a result, they also affect the tumor control and growth with autocrine and paracrine products. Lin and Karin (25) showed that different mediators that are released from these different cell types determine whether inflammation will have a tumor-initiating effect or anti-tumor activity. It was reported previously that inflammation plays roles in carcinogenesis and disease progression.

Lymphocytes are essential components of the cancer microenvironment contributing to carcinogenesis (26). In a study by Own by HE et al. (27) it was reported that the host, lymphocytes are primarily responsible for the anti-tumor immune response against tumor cells, lymphocytes cause cytotoxic cell death and cytokine production, inhibit the proliferation and metastatic activities of tumor cells, and the number of lymphocytes in the peripheral blood has important effects on the prognosis of breast cancer and the survival of the patient. It was shown in another study that in case of a decrease in the number of lymphocytes in the peripheral blood, an immune-tolerant microenvironment is formed around the tumor, and for this reason, lymphopenia has a poor prognostic effect (28).

In a study conducted by Ku GY et al.(29) it was found that the median survival of patients with a lymphocyte value above a thousand cells per ml in those receiving treatment for malignant melanoma was higher than those with a lymphocyte value below a thousand cells per ml. In an article that was published by Zhang GQ et al. (30) in March 2015, it was shown that the overall survival time is increased in patients with gastric cancer who are given activated autologous lymphocyte counts, and it was proven that the development of lymphopenia is directly related to the suppression of the immune system and is associated with a poor prognosis in many cancers.

Almost one third of cancer patients have thrombocytosis at diagnosis, and it was shown that abnormal activation of platelets is associated with CRC(31,32). Martin et al. (16) reportedin their studies that platelets play roles in tumor angiogenesis and invasion. They also reported that pro-inflammatory cytokines (IL-1, IL-2 and IL-6) increased platelet release after stimulating megakaryocytes in cancer patients. High platelet counts may be an indicator of exaggerated systemic inflammatory response in cancer patientsas an indicator of poor prognosis. Similar to neutrophils, platelets are also responsible for the release of various growth factors such as PDGF, PlateletFactor-4, TGF-B, VEGF and thrombospondin. These factors are involved in mitogen activation, proliferation of tumor cells, fusion of tumor cells, and growth and metastasis of the tumor mass. Platelets can release numerous growth factors to facilitate cancer growth and spread. Fidler et al. (33, 34) showed that platelets play important roles in tumor development and metastasis. They initiate tumor development by inducing angiogenesis via VEGF. They also reported that tumor cells adhere to other tumor cells

and platelets in their circulation. They argued that this may have important roles in tumor cell aggregation and tumor cell survival.

Orellana et al. (35) cultivated ovarian cancer cells with human platelets, and found that platelet-cancer interactions contributed to the formation of metastatic foci. Also, blocking key platelet receptors attenuated ovarian cancer metastasis. Templeton AJ et al. (36) published a meta-analysis of 20 studies in 2014, examined the relations between PLR-survival in different solid tumor types, and showed that high PLR level was associated with poor survival in pancreatic, colorectal, gastroesophageal, hepatocellular and ovarian cancer.

In the present study, no relations were found between lymphocyte count alone and prognosis. However, high platelet-lymphocyte ratios were found to be a poor prognostic factor. It was also found that a one-unit increase in PLR value increased the risk of death approximately one-fold.

Platelet size correlates with platelet activity, with larger platelets having more granules and secretory capacity. A relationwas detected between the platelet volume index and hematological diseases, thromboembolism, vascular diseases and some inflammatory diseases(37,38).

There are different opinions about the prognostic value of PDW in the literature. Zhang et al. and Huang et al. showed increased PDW as a poor prognostic factor in larynx and breast cancers, and other studies showed that decreased PDW is associated with a poor prognosis (39-42). It was shown in a study by Günaldı M, et al. (43) that increased PDW is associated with metastasis in gastric cancers. In our study, high platelet counts and PDW were associated with poor prognosis.

It was shown in a study showing that increased neutrophil count is associated with poor prognosis that cytokines responsible for hematopoiesis produced by tumor cells cause an increase in neutrophils in the peripheral blood, and this increase is also an indicator of aggressive tumor biology in neutrophils. It was shown that increased neutrophils cause remodeling in the extracellular matrix, initiate tumor development, play roles in metastasis, and suppress the T cell response by regulating the release of reactive oxygen products, nitric oxide and arginase (44). Consistent with this study, it was observed that survival was lower in our patients with high neutrophil counts.

PNI and LVI are the most evaluated prognostic parameters in pathology reports of various cancers. It was studied mostly in gastric and pancreatic cancers and was found to be associated with poor prognosis (45,46). Studies on colorectal cancer have shown that PNI is associated with poor prognosis (47,48). The relations of the scoring systems such as mGPS, SIS and PN Index with prognosis was investigated in many studies (49-51). In our study, the relations of these parameters with survival was not found to be statistically significant. In a study conducted by Wang F, et al. (52) in 2018, it was shown that the albumin-NLR inflammation score predicted the prognosis in CRC better than both SIS and mGPS. It was observed in our study that the prognosis of patients with low albumin value and high NLR value was worse.

There are some limitations in the present study. Being retrospective may cause some prejudices. The serum samples taken were not according to a certain standardization due to being retrospective. The small sampling size was another limitation. The inclusion of all colon and rectal cancers resulted in heterogeneity, and the recurrence rate was not given.

CONCLUSION

As a result, it is important to determine the risky stage II CRC patient group for which adjuvant chemotherapy will be beneficial. Currently, adjuvant chemotherapy is given to some risky stage II patient groups. However, it is not certain which stage II patient group will be given adjuvant chemotherapy and for how long. More study is needed. In the study, it was shown that PLR is a poor prognostic factor. We think that it would be more beneficial to administer adjuvant chemotherapy in the stage II CRC patient group with high PLR, and to give 6-month regimens instead of 3-month regimens in the stage III patient group.

Abbreviations: PLR: platelet-lymphocyte ratio, NLR: neutrophil-lymphocyte ratio, PDW: platelet distribution width, PNI: perineural invasion, LVI: lymphovascular invasion H&E: hematoxylinandeosin, IHC: immunohistochemistry, CRC: colorectal cancer, LMR: lymphocyte-monocyte ratio, MPGS: modified glasgow prognostic score, SIS: systemic inflammation score, PNindex: prognostic nutritional index

ETHICAL DECLERATIONS

Ethics Committee Approval: This study was approved by Tekirdağ Namık Kemal University Non-interventional Clinical Research Ethics Committee (Date: 25.01.2022, Decision No: 2022.05.01.05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancerstatistics. CA Cancer J Clin2012; 62: 10-29.
2. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008 Eur J Cancer 2010; 46: 765-81.
3. O'Connell JB, Maggard MA, Ko CY, Colon cancer survival rates with the new American Joint Committee on Cancer sixth editions taging. J Natl Cancer Inst 2004; 96: 1420-5.
4. Morris M, Platell C, de Boer B, et al. Population-based study of prognostic factors in stage II colonic cancer, Br J Surg 2006; 93: 866-71.
5. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004; 22: 1797-806.
6. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated within creasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089 J Clin Oncol 2003; 21: 2912-9.
7. Quah H.M, Chou J.F, Gonen M, et al. Identification of patients with high-risk stage II colon cancer for adjuvant therapy. Dis Colon Rectum 2008; 51: 503-7.
8. 8.HariDM, Leung AM, Lee JH, et al. AJCC Cancer Staging Manual 7th edition criteria for colon cancer: do the complex modifications improve prognostic assessment? J Am Coll Surg 2013; 217: 181–90.
9. Benson AB, 3rd, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004; 22: 3408–19.
10. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinicacid in colon cancer. Lancet 1995; 345: 939-44.
11. Figueredo A, CharetteML, Maroun J, et al. Adjuvant therapy for stage II colon cancer: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group J Clin Oncol 2004; 22: 3395-407.
12. Benson AB, Schrag B, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer J Clin Oncol 2004;22: 3408-19.
13. Van Cutsem E, Dicato M, Wils J, et al. Adjuvant treatment of colorectal cancer (current expert opinion derived from the Third International Conference: Perspectives in Colorectal Cancer, Dublin, 2001) Eur J Cancer 2002; 38: 1429-36.
14. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-relatedinflammation. Nature 2008; 454: 436– 44.
15. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? The Lancet 2001; 357:539-45
16. Martin HL, Ohara K, Kiberu A, Van Hagen T, Davidson A, Khattak MA, Prognostic value of systemic inflammation-based markers in advanced pancreatic cancer, Intern Med J 2014; 676-82.
17. Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, et al. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer J Gynecol Oncol 2012; 23: 265-73.
18. Asher V, Lee J, Innamaa A, et al. Pre operative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol 2011;13: 499-503.
19. Smith R.A, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductaladeno carcinoma. Am J Surg 2009;197: 466-72.
20. Kwon H.C, Kim S.H, OhS.Y.et al. Clinical significance of preoperative neutrophil-lymphocyt ever susplatelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers 2012; 17: 216-22
21. Itzkowitz SH, Rochester J. Colonic polypsand polyposis syndromes. In: Feldman M, Fiedman LS, Brandt LJ (Eds.) Gastrointestinal and Liver Disease. 8th Ed. 2713-2757, Saunders Elsevier, Philadelphia, 2006
22. Fry RD, Mahmoud N, Maron DJ, Ross HM. Colonand Rectum. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL (Eds.) Sabiston Textbook of Surgery. 18th Ed. 1348-1432, Saunders Elsevier, Philadelphia, 2008
23. Edwards BK, Howe HL, Ries LAG et al. Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on US cancer burden. Cancer 2002; 94: 2766-92
24. de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. Nat Rev Cancer 2006; 6: 24–37.
25. Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 2007; 117: 1175–83.
26. Hoffmann TK, Dworacki G, Tsukihiro T, Meidenbauer N, Gooding W, Johnson JT, Whiteside TL. Spontaneous apoptosis of circulating T lymphocytes in patients with head and neck cancer and its clinical importance. Clin Cancer Res 2002; 8: 2553–62.
27. Ownby HE, Roi LD, Isenberg RR, Brennan MJ. Peripheral lymphocyte and eosinophil counts as indicators of prognosis in primary breast cancer. Cancer. 1983; 52:126–30.
28. Ray-Coquard I, Cropet C, Van Glabbeke M, et al. Lymphopenia as a prognostic factor for overall lsurvival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res 2009: 69: 5383– 91.
29. Ku GY, Yuan J, Page DB, et al. Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. cancer 2010; 116: 1767–75.
30. Zhang GQ, Zhao H, Wu JY, et al. Prolonged overall lsurvival in gastric cancer patients after adoptive immunotherapy. World J Gastroenterol 2015; 21:2777-85.
31. Naschitz JE, Yeshurun D, Eldar S, Lev LM. Diagnosis of cancer-associated vascular disorders. cancer. 1996; 77: 1759–67.
32. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Preoperative thrombocytosis is associated with survival after surgery for colorectal cancer. J Surg Oncol 2012; 106: 887–91.
33. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 2003; 3: 453-8.
34. Grignani G, Falanga A, Pacchiarini L, et al. Human breast and colon carcinomas Express cysteine protein a seactivities with pro-aggregating and pro-coagulant properties. Int J Cancer 1988; 42: 554-7.
35. Orellana R. Kato S. Erices R, et al. Platelets enhance tissue factor protein and metastasis initiating cell markers, and act as chemoattractants increasing the migration of ovarian cancer cells. BMC Cancer2015; 15: 290
36. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014; 23:1204-12.
37. Mahdavi-Zafarghandi R, Shakiba B, Keramati MR, Tavakkoli M. Platelet volume indices in patients with varicocele. Clin Exp Reprod Med 2014; 41:92-95

38. Aliustaoglu M, Bilici A, Ustaalioglu BBO, et al. Theeffect of peripheral blood values on prognosis of patients with locally advanced gastric cancer before treatment. Med Oncol 2010; 27:1060–5.
39. Huang Y, Cui MM, Huang YX, et al. Pre operative platelet distribution width predicts breast cancer survival. Cancer Biomark 2018; 23: 205-11.
40. Zhang H, Liu L, Fu S Et al. Higher platelet distribution width predicts poor prognosis in laryngeal cancer. Oncotarget 2017; 8: 48138-44.
41. Cheng S, Han F, Wang Y Et al. The redistribution width and the platelet distribution width as prognostic predictors in gastric cancer. BMC Gastroenterol 2017; 17: 163.
42. Cui MM, Li N, Liu X, et al. Platelet distribution width correlates with prognosis of non-small cell lung cancer. SciRep 2017; 7: 3456.
43. Gunaldi M, Erdem D, Goksu S, et al. Platelet distribution width as a predictor of metastasis in gastric cancer patients. J Gastrointest Canc 2017; 48, 341–346.
44. Kemal Y, Yucel I, Ekiz K, Demirag G, et al. Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. Asian Pac J Cancer Prev 2014; 15:2651-4.
45. Bilici A, Seker M, Ustaalioglu BB, et al. Prognostic significance of perineural invasion in patients with gastric cancer who underwent curative resection. Ann Surg Oncol 2010; 17: 2037-44.
46. Chatterjee D, Katz MH, RashidA, et al. Perineural and intraneural invasion in post therapy pancreatic oduodenectomy specimens predicts poor prognosis in patients with pancreatic ductal adenocarcinoma Am J Surg Pathol 2012; 36: 409-17
47. Poeschl EM, Pollheimer MJ, Kornprat P, et al. Perineural invasion: correlation with aggressive pheno type and independent prognostic variable in both colon and rectum cancer J Clin Oncol 2010; 28: 358-60.
48. Liebig C, AyalaG, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. J Clin Oncol 2009; 27: 5131-7.
49. Park JH, Watt DG, Roxburgh CS, Horgan PG, McMillan DC. Colorectal Cancer, systemic inflammation and outcome: tumors taging and host staging. Ann Surg 2016; 263: 326–36.
50. Suzuki Y, Okabayashi K, Hasegawa H, et al. Comparison of prognostic scores based on preoperative inflammation in patients with Colorectal Cancer. Ann Surg 2016; 267: 52531
51. Nozoe T, Kohno M, Iguchi T, et al. The prognostic nutritional index can be a prognostic indicator in colorectal carcinoma. Surgery Today 2012; 42: 532-5.
52. Wang, F. He, W. Jiang, C. et al. Prognostic value of inflammation-based scores in patients undergoing radical resection for colorectal cancer. BMC Kanser 2018; 1102.

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Outcomes of patients coming to the emergency department after kidney transplantation

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ABSTRACT

Introduction: In kidney transplantation (KT) practice, improvements in patient care led to increased graft and patient survival. This study aimed to determine the symptomatology of KT patients presenting to emergency department (ED), their final diagnoses, and outcomes.

Material and Method: Data including demographic data (age and gender), chief complaints (CCs), number of ED presentations, ED presentation date, KT date, donor type (live/deceased), patient disposition (discharge/admission), final diagnosis, and outcomes (acute renal graft dysfunction/graft loss/death) were retrieved and analyzed.

Results: Twenty-five KT patients presented to ED during the study period. These patients presented to ED for 46 times with 50 CCs. Fever was the most frequent CC (20%). The ED presentation led to a final diagnosis of infection in 32 presentations (69.4%). The most frequent infection was urinary tract infection (UTI) (26.1%) followed, by acute gastroenteritis (17.4%) and upper respiratory tract infection (17.4%). Acute graft dysfunction was the most common "non-infectious diagnosis" (17.4%) followed by cardiovascular disease (8.5%). The ED presentation led to admission in 32.6% (15/46) of the cases. Among 15 admissions, 7 (46.7%) were due to UTI. No rejections, graft loss, or mortality occurred following any ED presentations.

Conclusion: When evaluating KT patients in the ED, physcians should bear in mind that they could have an infectious pathology that is often associated by fever, also they should check for acute graft dysfunction and cardiac pathologies.

Keywords: Emergency medicine, kidney transplantation, urinary infection, fever

INTRODUCTION

End-stage renal disease (ESRD) is rising in prevalence year after year (1,2). The rise in the predicted lifespan and the prevalence of systemic disorders such as diabetes mellitus and hypertension, both of which may result in ESRD, increased the overall number of individuals diagnosed with ESRD. Therefore, an increasing number of patients need renal replacement therapies (RRTs) (3). Although hemodialysis or peritoneal dialysis can be performed in patients with ESRD, it is widely accepted that kidney transplantation (KT) is the gold standard RRT method. In KT practice, the introduction of novel immunosuppression (IS) agents and improvements in postoperative patient care led to increased graft and patient survival.

On the other hand, these factors increased the utilization of emergency departments (ED) by KT recipients (4). These patients may present to ED due to either KT-related or KT-unrelated causes. However, emergency physicians should consider the fact that these patients are KT patients regardless of the chief complaint (CC) since these patients are on IS agents that are involved in various drug interactions and given for treating the CC may impair the graft function. Moreover, it should also be considered that IS may mask the classical signs of the condition (5). Therefore, emergency physicians should not only be familiarized with the emergency care of KT patients but also be familiar with their various presentations (3,5-20).

This study aimed to determine the symptomatology of KT patients presenting to ED, their final diagnoses, and outcomes in a newly established KT program.

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MATERIAL AND METHOD

The study was carried out with the permission of the University of Health Science Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Date: 14.06.2021, Decision No: 113-01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of the KT patients who presented to the ED between January 2017 and January 2021 were reviewed retrospectively. Patients who underwent KT at another transplant center and those with incomplete data were excluded. Demographic data (age and gender) of the patients and additional clinical data including CC, number of ED presentations, ED presentation date, KT date, donor type (live/deceased), patient disposition (discharge/admission), final diagnosis and outcome (acute renal graft dysfunction/graft loss/death) were retrieved from patients' electronic health records. We defined acute renal graft dysfunction or acute kidney injury (AKI) as the rise of serum creatinine level of ≥50% from baseline in the absence of an infectious diagnosis (4).

All data were entered into a previously composed database and they were analyzed by the Statistical Package for Social Sciences (SPSS 13.0) software. Data were presented as means±standard deviations or frequencies and percentages.

RESULTS

Our hospital KT program was established in January 2017. Twenty-seven KT cases were performed until January 2021. All KT patients were monitored by the same team, and they were all instructed to go to the same hospital's ED in the event of an emergency. While giving these directions, we considered the fact that family medical practice has not yet been established in Turkey and our KT program was a new program with a relatively low number of KTs. A retrospective assessment of medical records indicated that 25 of the 27 KT patients came to the ED during the research period. All KT patients were monitored by the same team, and they were all instructed to go to the same hospital's ED in the event of an emergency. While giving these directions, we considered the fact that family medical practice has not yet been established in Turkey and our KT program was a new program with a relatively low number of KTs. A retrospective assessment of medical records indicated that 25 of the 27 KT patients came to the ED during the research period The age range of the study patients was (25-67) with a mean of 48±13. Among these 25 patients, 19 (76%) were males while 6 (24%) were females 16 (64%). Live donor KT was performed in 16 (64%) cases, and 9 (36%) received deceased donor KTs. In total, these patients presented to ED for 46 times, corresponding to 1.84 ED presentations per KT patient (**Figure 1**).

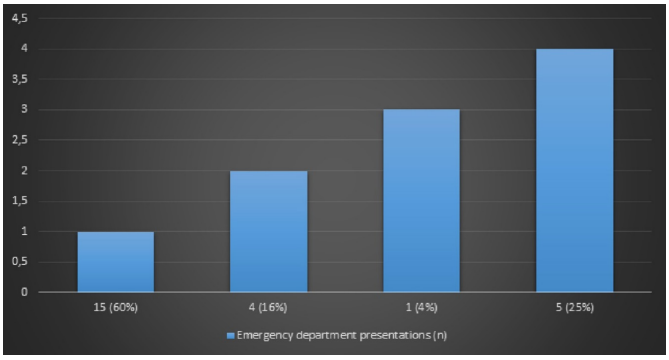

Figure 1. Distribution of patients as per number of emergency department presentations.

Among 25 KT patients, 3 (12%) developed delayed graft function (DGF). While 1 of these patients presented to ED for 4 times, the other two presented once and twice. During the 46 ED presentations, KT patients reported 50 CCs. These CCs and their rates are displayed in **Table 1.** Fever was the most frequent CC, followed by abdominal pain (20% and 16%).

Table 1. Frequency of chief complaints upon presentation to the emergency department

Chief complaint	Number (n)	Percentage (%)
Fever	10	20
Abdominal pain	8	16
Decreased oral intake	6	12
Diarrhea	5	10
Nausea/vomiting	5	10
Dysuria	4	8
Cough	2	4
Sore throat	2	4
Dyspnea	2	4
Hypertension	1	2
Headache	1	2
Chest pain	1	2
Backache	1	2
Wrist pain	1	2
Rectal bleeding	1	2

The time interval between KT and ED presentation was (14-1159) days. The final diagnoses of the patients are shown in **Table 2**.

Table 2. Final diagnoses of the patients

Infectious diagnoses	Number (n)	Percentage (%)
Urinary tract infection	12	26.1
Acute gastroenteritis	8	17.4
Upper respiratory tract infection	8	17.4
Lower respiratory tract infection	4	8.5
Total	32	69.4
Non-infectious diagnoses	**Number (n)**	**Percentage (%)**
Acute kidney injury	8	17.4
Cardiovascular disease	4	8.5
Wrist fracture	1	2.3
Hemorrhoids	1	2.3
Total	14	30.6

The ED presentation led to a final diagnosis of infection in 32 among 46 presentations (approximately 69.4%). The most frequent infection was UTI (26.1%) followed by AGE (17.4%) and URTI (17.4%). None of the respiratory tract infections encountered in our series was diagnosed with coronavirus disease-2019 (COVID-19). Acute renal graft dysfunction or AKI was the most common diagnosis in the "non-infectious diagnoses" category, with a rate of 17.4%. It was followed by CVD (8.5%). Our analysis elucidated that 32.6% (15/46) of the ED presentations were followed by admission of the patient. Among these 15 admissions, 7 (46.7%) were due to UTI. Seven of 12 patients diagnosed with UTI (58.3%) were admitted.

In this cohort, the remaining 8 of 15 patients who were admitted were diagnosed with AGE (3/15, 20%), LRTI (2/15, 13.3%), AKI (2/15, 13.3%), and wrist fracture (1/15, 6.7%). No rejections, graft loss, or mortality occurred following any ED presentations.

DISCUSSION

Both the number of KT cases and the survival rate of kidney grafts are growing globally (1). As a result, the likelihood of an emergency physician seeing a KT patient increases. Due to the fact that KT patients are a vulnerable patient group on continuous IS, they may come to the ED with a broad variety of symptoms (4). These patients have a low threshold for coming to the ED, since transplant teams instruct them to prioritize any uncommon symptoms and to present to either the transplant outpatient clinic or the ED, depending on the time of presentation (working hours vs. out of working hours). This strategy is more prevalent in nations or places where family medicine is still in its infancy (7). Additionally, newly formed transplant centers may use the same strategy, since KT team members feel more secure knowing that their patients will get treatment on schedule. Regardless of the reason for this practice, it places an additional stress on emergency doctors. Therefore, emergency doctors must be conversant with the symptomatology of KT patients who present to EDs, the most often encountered diagnoses, and their outcomes.

It is known that IS paves the way for infectious diseases, and KT patients may be affected by either opportunistic or non-opportunistic infections (4). Tokalak et al. (7) reviewed the data of 78 KT patients who presented to ED and reported that the most frequent CC was fever (26.9%) and the most frequent diagnosis was infection in their series. The admission rate was 57.7% in this cohort. Infection was also the most common diagnosis (77.8%) among those who were admitted. Our findings are in line with this study. Fever was the most common CC (20%) in our series. Moreover, infectious diagnoses were more common than non-infectious ones both in our entire cohort (69.4 vs. 30.4%) and among those admitted to the hospital. However, our admission rate (i.e. 32.6%) was lower than the rate reported by Tokalak et al. (7), and respiratory tract infections were more frequently diagnosed than UTI (54.2 vs. 5.7%) in their study. While evaluating these results, it is necessary to consider the sample sizes of the two research (78 vs. 25)

Kartal et al. (3) evaluated data from 163 KT patients who reported to the ED. They noticed that UTI was the most often diagnosed condition in their series (16.6 percent). Their admission rate was 40%, and they admitted 59.3 percent of patients diagnosed with UTI. UTI was followed by URTI (12.3 percent) and AGE in this dataset (11.7 percent). According to these experts, KT patients with UTI and systemic manifestations such as fever and tachycardia should be hospitalized. Our methodology and conclusions paralleled those of Kartal et al (3). The most frequently diagnosed conditions in our series were likewise UTI, URTI, and AGE, and the admission rates were comparable across the two studies (40 vs. 32.6 percent). Notably, two investigations found identical admission rates for individuals diagnosed with UTI (59.3 vs. 58.3 percent). Kartal et al. (3) reported admitting five of fourteen (35.7 percent) patients with AGE. We admitted three out of eight (37.5%) individuals diagnosed with AGE. Kartal et al. (3) recommended that KT patients identified with AGE at the ED be hospitalized if they were dehydrated as a result of diarrhea or poor oral intake. In this way, our methodology was comparable to that of Kartal et al. (3). The closeness in admission rates for individuals with AGE across the two trials is most likely owing to the identical methodology.

Uysal et al. (6) reviewed the data of 41 patients who presented to ED. These authors denoted that the most common CC was fever (36.6%) and infectious diagnoses were more common than non-infectious ones (68 vs. 32%). Among the infectious diagnoses, AGE was the most common (26.8%) and it was followed by URTI (21.9%) and UTI (9.7%). On the other hand, AKI was the most frequent non-infectious diagnosis (9.7%). Our findings are similar to this study since fever was also the most frequent CC, infection was the most frequent diagnosis and AKI was the most common non-infectious diagnosis in our cohort. Uysal et al. (6) reported that they admitted 73.1% of their patients. This admission rate is significantly higher than our admission rate and those reported by other centers (3,7). However, these authors stated that their admission threshold was too low since they preferred to follow their KT patients as inpatients rather than outpatients following presentation to ED

(6). Uysal et al. (6) also reported that 2 (4.8%) patients presented with wrist fractures. In our cohort, 1 (2.3%) of our patients presented to ED with a wrist fracture. It is known that wrist fractures can be due to osteoporosis (9). All patients in our cohort, including this particular patient, were on an IS regime consisting of tacrolimus, mycophenolate mofetil, and prednisone. This patient was a postmenopausal woman who received a deceased donor KT in the first year of our KT program and experienced a low-trauma wrist fracture. Prednisone and tacrolimus can lead to bone loss averaging 1 to 2% per year after transplant. This patient was consulted with orthopedic surgery and received treatment for osteoporosis after fixation of the wrist fracture.

Uysal et al. (6) reported that 1 (2.4%) of their patients presented to ED with chest pain and were diagnosed with supraventricular tachycardia. In our cohort, 4 patients visited ED with the suspicion of an acute coronary syndrome. Two of these patients had dyspnea, 1 had a sore throat, and 1 had chest pain as the CC. Although none of these patients withouta history of CVD were diagnosed with myocardial infarction or cardiac arrhythmia in the ED setting, they were diagnosed with CVD after elective cardiac investigations (8.5%). The relatively higher diagnosis rate of CVD in our series (8.5 vs. 2.4%) can be due to the difference between the two patient groups regarding the primary diseases. The primary reason for ESRD was not analyzed in our cohort and also in the study of Uysal et al. (6). However, it is known that KT leads to a 5-fold increase in the risk of CVD (4).

To the best of our knowledge, this study is the first study analyzing the ED data of the KT patients transplanted in a newly established program. In line with this, patients were instructed to present to ED if they had unusual complaints out of work hours or in case of an emergency. Thus patients had a low threshold for presenting to ED.

CONCLUSION

After weighing our data, we believe that fever is the most often seen CC and infections, especially UTIs, are the most frequently encountered diagnosis in KT patients arriving to the ED. AKI is the most prevalent clinical condition among non-infectious diagnoses. Emergency doctors should keep in mind that KT patients may arrive to the ED with a number of symptoms, including dysuria and wrist discomfort, and may be diagnosed with a variety of conditions, including UTI and wrist fractures. Our study has some limitations which need to be considered while evaluating its findings. First, it is a retrospective study. Second, it has a relatively small sample size. Third, data regarding renal graft function at the time of ED presentation were not included in the analysis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the University of Health Science Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (Date: 14.06.2021, Decision No: 113-01).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study had received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Collins AJ, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. Am J Kidney Dis 2010; 55: S1-420, A6-7.
2. Cimen SG, Oğuz E, Gundogmus AG, Cimen S, Sandikci F, Ayli MD. Listening to music during arteriovenous fistula surgery alleviates anxiety: A randomized single-blind clinical trial. World J Transplant 2020; 29: 79-89.
3. Kartal M GE, Eray O, Gungor F. Factors affecting to hospital admission for renal transplant patients in the emergency department. Turk J Emerg Med 2009; 9: 159–62.
4. Venkat KK, Venkat A. Care of the renal transplant recipient in the emergency department. Ann Emerg Med 2004; 44: 330-41.
5. Bardaxoglou E, Maddern G, Ruso L, et al. Gastrointestinal surgical emergencies following kidney transplantation. Transpl Int 1993; 6: 148-52.
6. Uysal E, Dokur M, Bakir H, Ikidag MA, Kirdak T, Kazimoglu H. the reasons of renal transplant recipients' admission to the emergency department; a case series study. Emerg (Tehran) 2016; 4: 207-10.
7. Tokalak I, Başaran O, Emiroğlu R, Karakayali H, Bilgin N, Haberal M. Problems in postoperative renal transplant recipients who present to the emergency unit: experience at one center. Transplant Proc 2004;36:184-6.
8. Trzeciak S, Sharer R, Piper D, et al. Infections and severe sepsis in solid-organ transplant patients admitted from a university-based ED. Am J Emerg Med 2004; 22: 530-3.
9. Heaf JG. Bone disease after renal transplantation. Transplantation. 2003; 75: 315-25.
10. Grimaldi A, Barletta A, Rascente M, et al. Infectious complications in the renal transplant recipient. Transplant Proc 2005; 37: 2502-3.
11. Koo EH, Jang HR, Lee JE, et al. The impact of early and late acute rejection on graft survival in renal transplantation. Kidney Res Clin Pract 2015; 34: 160-4.
12. Schmaldienst S, Dittrich E, Hörl WH. Urinary tract infections after renal transplantation. Curr Opin Urol 2002; 12: 125-30.
13. Becker S, Witzke O, Rübben H,et al. Harnwegsinfektionen nach Nierentransplantation: Essener Algorithmus zur kalkulierten Antibiotikatherapie [Urinary tract infections after kidney transplantation: Essen algorithm for calculated antibiotic treatment] Urologe A 2011; 50: 53-6.

14. Unterman S, Zimmerman M, Tyo C, et al. A descriptive analysis of 1251 solid organ transplant visits to the emergency department. West J Emerg Med 2009; 10: 48-54.
15. McElroy LM, Schmidt KA, Richards CT, et al. Early postoperative emergency department care of abdominal transplant recipients. Transplantation 2015; 99: 1652-7.
16. Schold JD, Elfadawy N, Buccini LD, et al. Emergency department visits after kidney transplantation. Clin J Am Soc Nephrol 2016; 11: 674-83.
17. Li AH, Lam NN, Naylor KL, et al. Early hospital readmissions after transplantation: burden, causes, and consequences. Transplantation 2016; 100: 713-8.
18. Okidi OO, Van Dellen D, Sobajo C, et al. Kidney transplant recipients requiring critical care admission within one year of transplant. Exp Clin Transplant 2017; 15: 40-6.
19. Weeda ER, Su Z, Taber DJ, et al. Hospital admissions and emergency department visits among kidney transplant recipients. Clin Transplant 2019; 33: e13522.
20. Lovasik BP, Zhang R, Hockenberry JM, et al. Emergency department use among kidney transplant recipients in the United States. Am J Transplant 2018; 18: 868-80.

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Comparison of thyroid scintigraphy and ARFI-elastography in autoimmune thyroid diseases

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ABSTRACT

Aim: To compare the ARFI elastographic and scintigraphic quantitative data obtained from thyroid gland and to evaluate diagnostic value of ARFI elastographic measurements in autoimmune thyroid diseases.

Material and Method: In the study a total of 61 patients (41 women, 20 men) including 24 Graves' disease, 15 Hashimoto disease and 22 control subjects. The patients mean age was 33.9±10.9 years. Patients with thyroid nodules were not included in the study. Thyroid uptake was performed with Tc 99m pertechnetate and the elastosonography score of the thyroid gland was determined with ARFI. Findings of both disease groups were statistically compared with each other and control group

Results: For thyroid uptake test; a statistically significant difference was found between two disease ($p < 0.001$) and between each disease and control group ($p < 0.001$ for Hashimoto, $p < 0.001$ for Graves). However, for ARFI method; a statistically significant difference was not found between two disease ($p=0.336$) and between each disease and control group ($p=0.14$ for Hashimoto, $p=0.08$ for Graves).

Conclusion: Thyroid scan and thyroid uptake measurements are extremely valuable in differential diagnosis of autoimmune thyroid diseases and ARFI elastosonographic measurements don't seem to replace scintigraphic datas.

Keywords: Thyroid scintigraphy, thyroid uptake, ARFI, Graves' disease, Hashimoto's thyroiditis

INTRODUCTION

Autoimmune thyroid diseases are common in the population, thyroid scintigraphy and thyroid uptake studies are the most important diagnostic methods used in the differential diagnosis of these diseases.

Thyroid uptake studies with I-131 and I-123 have taken their place in the literature with their success in the differential diagnosis of autoimmune thyroiditis (1-6). A high degree of correlation was observed between thyroid uptake studies with Tc 99m pertechnetate and studies with radioactive iodine (7-9). Tc 99m pertechnetate is inexpensive, easily available and easily applied. Its radiation dose is low and the absence of beta (β) rays makes it more useful than radioactive iodine (9).

Ultrasonography contributes to the differential diagnosis of autoimmune thyroid diseases with additional modalities such as doppler. Elastography is one of the latest developments in ultrasound technology, which was developed in 1990-1991. It measures tissue stiffness quantitatively and qualitatively with sound waves method. Initially, the 'strain' data of the tissue were obtained by applying a certain amount of pressure. Low-strain areas given lighter values and high-strain areas given darker values in grayscale elastogram. With the contribution of computer algorithms and innovative technological developments, high quality qualitative color overlay elastograms obtained. Recently, quantitative analysis methods such as Acoustic radiation force impulse (ARFI), Shear wave elastography and Real-time elastography have been developed (10). ARFI is a new USG modality in which tissue stiffness is quantitatively measured by taking into account the velocity of sound wave propagation in the tissue (11-12).

In previous studies, it was observed that ARFI elastography scores increased in Hashimoto thyroiditis (HT) and Graves diseases (GD) compared to control groups. However, statistically, both diseases could not be differentiated from each other, in some studies, the elasticity values of GD were

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found to be higher (13-15). In some studies the elasticity values of HT were higher (16). Our purpose is to compare Tc 99m thyroid uptake values and ARFI elastography scores of patients diagnosed with HT and GD, with control groups and each other and to present the imaging findings of these diseases by both methods.

MATERIAL AND METHOD

The present prospective study was carried out with the permission of Dicle University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (Date: 26.12.2014, Decision No: 273). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study we included subjects with HT and GD were selected from the patients who underwent a diagnosis of autoimmune thyroiditis and thyroid scintigraphy and thyroid uptake in Dicle University Medical Faculty Hospital in a two year period. The control group was selected from patients who came to the salivary gland and parathyroid scintigraphy between the same dates, but were clinically and laboratory normal in terms of thyroid diseases. After being eliminated the patients with thyroid nodüles, totally 61 subjects (41 women, 20 men) included in the study. Of which 24 Graves' disease, 15 Hashimoto disease and 22 control group. The mean age of patients was 33.9±10.9 years. The reason why they were included in the study was explained by the researcher physician and their written consent was obtained.

Attention was paid to the preparation of patients for thyroid uptake study. The thyroid uptake test was performed on the 2012 model Brightview gamma camera system (Philips Medical Systems, Eindhoven, the Netherlands). The filled injectors of the patients (5 mCi Tc 99m pertechnetate) were counted for 30 seconds in anterior position at 10 cm distance with parallel hole general purpose collimator (LEGP). Empty injectors were also counted for 30 seconds after injection. In the 20th minute, 5-minute shots were taken at a distance of 10 cm with the parallel hall collimator in supine position and the neck in extension. The calculations of the thyroid uptake study were made at the Xeleris 2011 model workstation of General Electric with the thyroid uptake program. After the full injectors, empty injectors and anterior images of the patients were introduced to the device, ROIs (Region of Interest) were drawn manually around the thyroid gland. The ROI, which the device automatically draws in the neck area immediately inferior after separating both lobes, was used for background correction (**Figure 1**). Then, uptake values were obtained by using automatic calculation (via thyroid uptake formula given in the general information section), both thyroid lobes separately and total. Those with an uptake value less than 0.3% were considered to be decreased, those between 0.3% and 3.75% were considered normal, and those greater than 3.75% were considered increased (8,9).

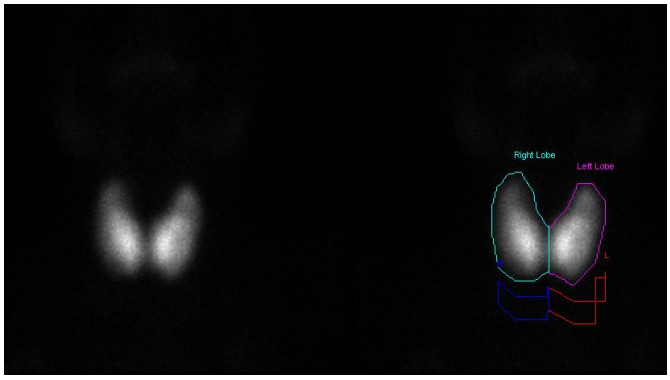

Figure 1. Drawing of both thyroid lobes and background in thyroid uptake study

ARFI imaging was performed on the same day by the experienced radiologist at Dicle University Medical Faculty Hospital Radiology Clinic. Patients with nodules in the gland were excluded by routine USG on the thyroid gland prior to ARFI imaging. The imaging procedure was performed in a supine position using the ACUSON S2000 ultrasound system (Siemens, California, US) linear probe (4–9 MHz) and a sufficient amount of ultrasound gel. Considering that it may affect the elasticity results, excessive pressure was avoided while using the probe and care was taken to ensure that the applied pressure was at a standard level in each case. SWI (shear wave velocity: tissue spread rate) was calculated in m/s by placing ROIs in the thyroid gland parenchyma. Attention was paid to keep the areas where ROI was drawn in the parenchyma. Major vascular structures within the thyroid parenchyma and soft tissues around the parenchyma were ruled out (**Figure 2**). Five AFRI values were obtained from the right thyroid lobe, five from the left lobe and one from the isthmus. Mean ARFI of thyroid gland was obtained by taking the average of these.

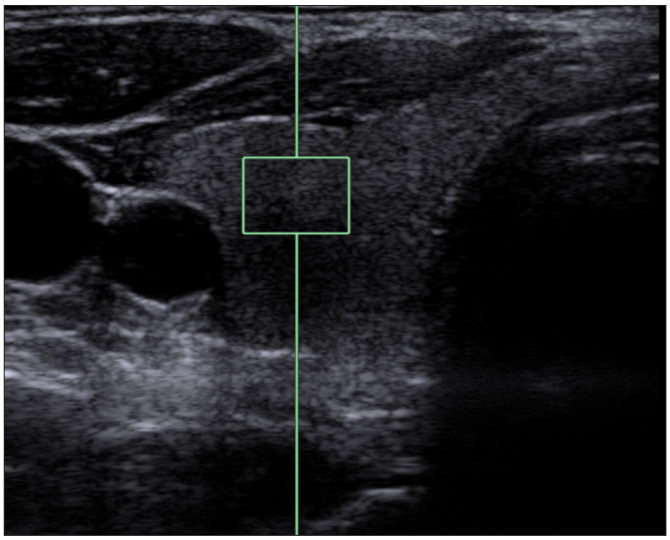

Figure 2. Obtaining ROI and ARFI values placed in thyroid parenchyma

Statistical Analysis

All statistical analyzes were done using SPSS 15.0 program. P <0.05 was considered statistically significant. The data were classified according to their numeric or nonnumeric distribution. Suitable parametric or nonparametric tests were used. Data compared using Kruskal Wallis, ANOVA and Stundient's t tests.

RESULTS

The mean age of patients between the ages of 18-65 was measured as 33.9±10.9. The mean age of GD was 34.8±11.3, and 67% of the patients were women. The mean age of HT patients was 26.5±6.6 and 75% of the patients were women. The mean age of the control group was 37.9±10.6 and 75% of the patients were women. The mean Tc 99m uptake value was 5.07±6.05% and the mean ARFI value was measured as 1.82±0.38. A statistically significant difference was found between Tc 99m Uptake values for GD and control group, HT and control group, and GD and HT; (p <0.001) (**Figure 3**).

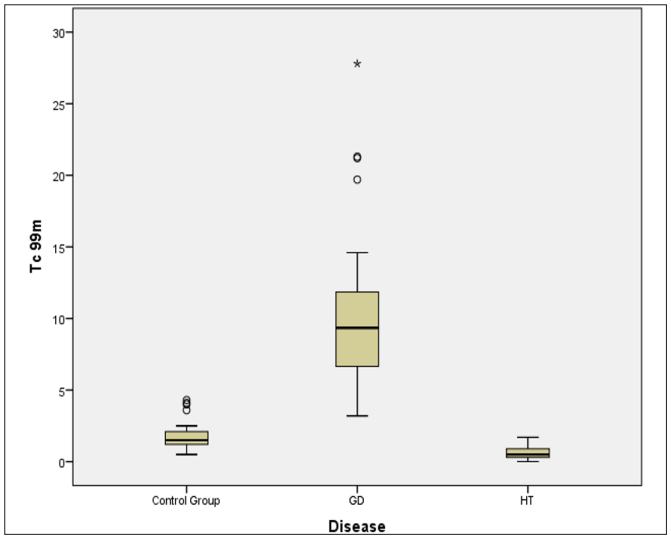

Figure 3. Tc 99m Uptake distribution of Control Group, GD and HT

The sensitivity of the thyroid uptake test performed with Tc 99m Perteknetat to predict GD and HT from each other was 100%, the sensitivity to predict GD from the control group was 95.8% and the sensitivity to predict HT from the control group was 60%.

There was no significant difference in the comparison between ARFI elastography values for GD and control group (p: 0.08), HT and control group (p: 0.14), GD and HT (p: 0.336). When the ARFI elastography values of the whole patient group were compared with the ARFI elastography values of the control group, no significant difference was observed (p: 0.09) (**Figure 4**).

A weak correlation was detected between Tc 99m pertechnetate uptake values and ARFI values (p: 0.048, r: 0.255) (**Figure 5**).

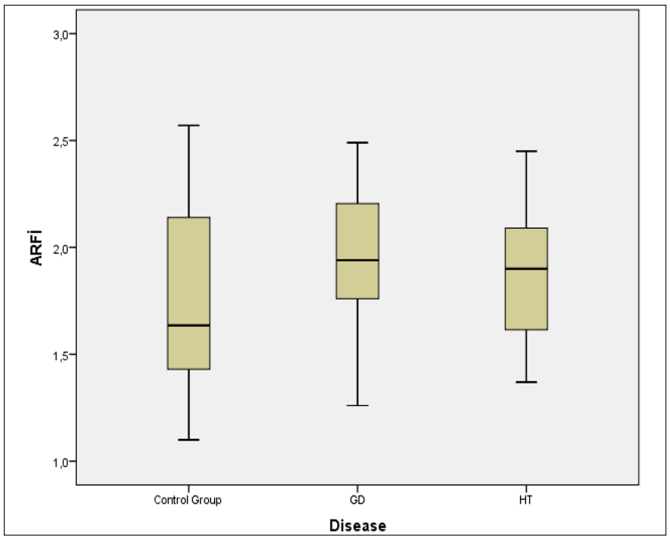

Figure 4. The distribution of ARFI values of Control Group, GD and HT

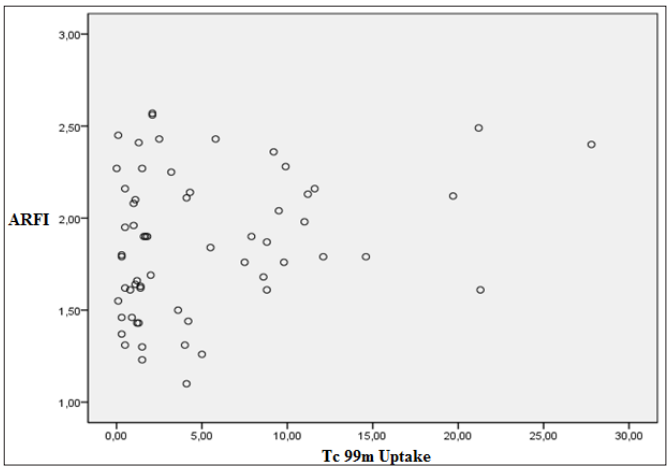

Figure 5. Correlation Between Tc 99m Pertechnetate Uptake Value and ARFI Elastography Values

DISCUSSION

In the differential diagnosis of autoimmune thyroid diseases, thyroid uptake test and thyroid scintigraphy are very valuable diagnostic methods used in the routine. RAIU test is one of the most important methods used in routine using I-131 and I-123 in the differential diagnosis of thyrotoxicosis. The fact that Tc 99m Perteknetat is inexpensive, easily available and easily applied, its radiation dose is low, and the absence of β rays makes it more attractive than radioactive iodine (9). In the thyroid uptake study conducted by Sostre et al. (7) using a group of 123 patients, using Tc 99m Pertechnetate and I-131, the uptake values of Tc 99m Pertechnetate correlated with I-131 at a rate of 89%. As a result of the study of Ramos et al. (17), group of 47 euthyroid patients; stated that Tc 99m Pertechnetate is the most suitable option for thyroid scintigraphy and thyroid uptake study due to its low radiation dose, ease of application and cheapness.

The sensitivity and specificity of the Tc 99m Uptake test they studied in 15 pediatric patients diagnosed with Duck and Sty's (18) GD were higher than 90%. In the study where Zuhur et al (19) compared Color Doppler USG, Tc 99m Uptake and TRAb values in 150 GD, 79 silent thyroiditis patients and 71 euthyroid patients; The separation sensitivity and specificity of these three groups of the Tc 99m Uptake test were found to be 90.7% and 89.9%, respectively. As stated in these studies, the success of the Tc 99m Thyroid Uptake test in GD has taken its place in the literature. Similarly, in our study, the sensitivity of this test to GD and HT from each other was 100%, and the sensitivity to differentiate Graves patients from control group was 95.8%.

Thyroid scintigraphy and Thyroid Uptake studies in HT vary according to the stage of the disease. In the early period of the disease, that is, when the atrophy does not start in the thyroid parenchyma, uptake studies are followed within normal limits. In the late period, atrophy begins and the cell reserve begins to decrease and the follicles are replaced by fibrotic tissues (20). During this period, uptake values begin to decrease. The sensitivity of our study to differentiate HT and control group was 60%. HT cases with uptake values within normal limits may be due to early stage of disease.

In the literature, although GD and HT can be seen at any age, it has been reported that it occurs most frequently between the ages of 20-40 and is observed 3-8 times more in women than in men (21-25). Similar to the literature in our study; the mean age of GD patients is 34.8±11.3, 67% of the patients are women, while the mean age of HT patients is 26.5±6.6, 75% of the patients are women.

Traditionally in HT and GD, the gland is said to have diffused somewhat diffusely and acquired a tire consistency. ARFI-elastography evaluates tissue stiffness quantitatively and current studies in this field are ongoing. In a study by Sporea et al. (13) ARFI values of thyroid gland were evaluated in a group of 136 patients. Of these, 44 are healthy, 48 are GD, 37 are HT, 4 are diffuse goiter and 1 are amiodarone-related thyroiditis. In this study, it was reported that ARFI values were higher in GD and HT compared to the healty population and that they could predict these two groups statistically from the healthy population. In another study by Sporea et al. (14) of 74 people, 23 of them were normal, 29 of them were GD and 22 of them were HT. ARFI values of GD and HT were higher than the control group. Rahatlı et al. (15) in a study where they evaluated Shear wave elastography with 30 HT patients, 22 GD patients and 30 healthy patients; Shear wawe velocite values have been reported to be higher in GD and HT compared to the healthy population. Although not statistically significant, in our study, ARFI values of GD and HT were slightly higher than the control group. The probable reason that these differences could not be confirmed statistically may be the low number of cases in our patients and control group (Graves: 24, Hashimoto: 15, control: 22). If we could increase the number of cases in our patients and control group to over 30; we could possibly detect statistically significant differences for these comparisons in our study as well. However, due to the limited working time, we could not reach the desired numbers.

In the same studies of Sporea et al. (13) and Rahatlı et al. (15); reported that ARFI and Shear wave velocite values of the thyroid gland are slightly higher in GD than HT, but GD and HT were not statistically differentiated. Although not statistically significant in our study, ARFI values of GD was slightly higher than the HT. However, in the elastography study of Wee et al. (16) with a group of 34 patients, including 15 GD, 3 HT, 1 diffuse goiter patient and 15 control groups; the elasticity of the gland was found to be higher in HT than in GD. The fact that the number of Hashimotos in the work of Wee et al. was limited to only 3 cases may have caused this difference.

In the literature, current studies with Shear Wave Elastography and Real-Time Elastography; in HT and GD, the elasticity values were increased as compared to the healthy patients (26-32).

In study by Sporea et al (13); the mean ARFI value for GD was 2.62±0.58, and the mean ARFI value for HT was 2.34±0.61 and the mean ARFI value was 1.98±0.37 for the control group. In addition, both convex and linear USG probes were used in their studies and in their comparison; stated that the use of convex or linear USG probes did not change ARFI values in all three patient groups. In study by Fukuhara et al. (26) using a linear probe; the mean ARFI value for HT was 2.56±0.57 and 1.59±0.41 for the control group. In our study, we used a linear USG probe and found the mean ARFI value of 1.96±0.32 for GD, 1.87±0.31 for HT, and 1.75±0.46 for the control group. It is noteworthy that the mean ARFI values of all patient groups in these two studies were higher than in our study. Although we all worked with the same device, the different results cause of the application differences during the measurements. One of these application differences is the pressure difference applied to the probe while ARFI measurements are made. While we were making ARFI measurements, we applied as little pressure on the probe as we thought it might affect the stiffness of the tissue. However, in the other two studies, the pressure applied to the probe during the measurements was not specified, and a possible high pressure that they may have applied may result in higher results in the measurements. In addition, unlike our other study, measurements were not taken from isthmus in the other two studies. The measurements we take from istmus may have reduced our measurement averages.

In our study; we found a weak correlation between Tc 99m Pertechnetate uptake value and ARFI scores. We have not encountered any previous study in the literature on this subject. However, the number of patients in the HT group of this correlation (15); We attributed it to less than the GD (24) and control groups (22). Because, in the Tc 99m uptake test, the results of Graves patients were found higher than the control group, while the results of HT patients were lower than the control group. However, in our ARFI measurements, both the Graves group and the Hashimoto group were higher than the control group. If the HT group in our study was slightly higher in number, it would affect our correlation analysis negatively and perhaps we would not find the weak correlation we obtained.

CONCLUSION

In the differential diagnosis of autoimmune thyroid diseases; Thyroid scintigraphy and thyroid uptake data with Tc 99m Pertechnetate are very valuable. The role of ARFI elastography in the differential diagnosis of autoimmune thyroid diseases seems to be limited for now, more studies are needed to evaluate the contribution of this method.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dicle University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (Date: 26.12.2014, Decision No: 273).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study had received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Görpe A, Cantez S. Endokrin sistem. Pratik Nükleer Tıp; 1. Baskı, 195-219, İstanbul Tıp Fakültesi Vakfı, İstanbul, 1992.
2. Erdoğan G, Kamerl N, Başkal N, et al. Klinik Endokrinoloji. Antıp AŞ, Ankara, 1997: 67-118.
3. Mettler FA, Guiberteau MJ. Essentials of nuclear medicine imaging, Fifth ed. WB Saunders Company, Philadelphia, 2005.
4. Freitas JE, Gross MD, Sarkar S. Laboratory (in vitro) assesment of thyroid function. Diagnostic Nuclear Medicine, Sandler MP, Coleman RE, Patton JP, Wackers FJ, Gottschalk A. Fourth ed. Vol. I, 591-606, Lippincott Williams and Wilkins, Philadelphia, 2003.
5. Orgiazzi J. Anti-TSH receptor antibodies in clinical practice. Endocrinol Metab Clin North Am 2000; 29: 339-vii.
6. Martin WH, Sandler P. Thyroid imaging. diagnostic nuclear medicine, Sandler MP, Coleman RE, Patton JP, Wackers FJ, Gottschalk A. Fourth ed. Vol. I, 607-51, Lippincott Williams and Wilkins, Philadelphia, 2003.
7. Sostre S, Parikh S. A visual index of thyroid function. Clin Nucl Med 1979; 4: 59-63.
8. Burke G, Halko A, Silverstein GE, Hilligoss M. Comparative thyroid uptake studies with 131 I and 99m TcO 4. J Clin Endocrinol Metab 1972; 34: 630-7.
9. Higgins HP, Ball D, Eastham S. 20-min 99m Tc thyroid uptake: a simplified method using the gamma camera. J Nuc Med 1973; 14: 907-11.
10. Garra BS. "Elastography: current status, future prospects, and making it work for you," Ultrasound Quarterly 2011; 27: 177–86.
11. Bojunga J, Dauth N, Berner C, et al. Acoustic radiation force impulse imaging for differentiation of thyroid nodules. PLoS One 2012; 7: e42735.
12. Grazhdani H, Cantisani V, Lodise P, et al. Prospective evaluation of acoustic radiation force impulse technology in the differentiation of thyroid nodules: accuracy and interobserver variability assessment. J Ultrasound 2014; 17: 13–20.
13. Sporea I, Sirli R, Bota S, Vlad M, Popescu A, Zosin I. ARFI elastography for the evaluation of diffuse thyroid gland pathology: Preliminary results. World J Radiol 2012; 4: 174–8.
14. Sporea I, Vlad M, Bota S, et al. Thyroid stiffness assessment by acoustic radiation force impulse elastography (ARFI). Ultraschall in der Medizin 2011; 32: 281–5.
15. FK Rahatlı, H Turnaoğlu, NG Kırnap, et al. Value of shear wave elastography by virtual touch tissue imaging quantification in patients with diffuse thyroid gland pathology. Turk J Med Sci 2018; 48: 993-8.
16. Wee S, Jeon SJ, Choi SS. Iksan-si/KR. Shear wave elastography for the evaluation of diffuse thyroid gland pathology: preliminary results, ECR, poster number; C-0495, 2014.
17. Ramos CD, Wittmann DEZ, Etchebehere ECSDC, Tambascia MA, Silva CAM, Camargo EE. Thyroid uptake and scintigraphy using 99mTc pertechnetate: standardization in normal individuals. Sao Paulo Med J/Rev Paul Med 2002; 120: 45-8.
18. Stephen C. Duck, J. Sty. Technetium thyroid uptake ratios in pediatric Graves Disease. J Pediatr 1985; 107: 905-9.
19. Zuhur S, Ozel A, Kuzu I, et al. The diagnostic utility of color doppler ultrasonography, Tc-99m pertechnetate uptake, and TSH-receptor antibody for differential diagnosis of graves' disease and silent thyroiditis: a comparative study. Endocr Pract 2014; 20: 310-9.
20. Hayashi Y, Tamai H, Fukata S, et al. A long-term clinical, immunological, and histological follow-up study of patients with goitrous chronic lymphatic thyroiditis. J Clin Endocrinol Metab 1985; 61: 1172–8.
21. Jackson IMD, Hennessey JV, Thyroiditis. In: Becker KL, editors. Principles and practice of endocrinology and metabolism. Third edition. Lippincott Williams & Wilkins. 2001; 456-8.
22. Wang C, Crapo LM. The epidemiology of thyroid disease and implications for screening. Endocrinol Metab Clin North Am 1997; 26: 189- 218.
23. Tunbridge WM, Vanderpump MP. Population screening for autoimmune thyroid disease. Endocrinol Metab Clin North Am 2000; 29: 239- 53.
24. O'Donnell AL. Hyperthyroidizm: systemic effects and differential diagnosis. Falk SE Thyroid Disease. 2nd ed. Philadelphia: Lippincott Raven 1997;14: 241-52.
25. Hanks JB. Thyroid. Sabiston D.C (ed). Textbook of Surgery. 16th ed. Philadelphia: WB Saunders Comp 2001; 603-28.

26. Fukuhara T, Matsuda E, Izawa S, Fujiwara K, Kitano H. Utility of shear wave elastography for diagnosing chronic autoimmune thyroiditis. J Thyroid Res 2015; 164548: 5.
27. Menzilcioglu MS, Duymus M, Gungor G, et al. The value of real-time ultrasound elastography in chronic autoimmüne thyroiditis. Br Institute Radiol 2014; 07.
28. Magri F, Chytiris S, Capelli V, et al. Shear wave elastography in the diagnosis of thyroid nodules: feasibility in the case of coexistent chronic autoimmune Hashimoto's thyroiditis. Clin Endocrinol 2012; 76: 137–41
29. Vlad M, Golu I, Bota S, et al. Real-time shear wave elastography may predict autoimmune thyroid disease. Wiener klinische Wochenschrift 2015; 127: 330-6.
30. Kim I, Kim EK, Yoon JH, Son EJ, Moon HJ, Kwak YJ. Diagnostic role of conventional ultrasonography and shearwave elastography in asymptomatic patients with diffuse thyroid disease: initial experience with 57 patients. Yonsei Med J 2014; 55: 247-53.
31. Kara T, Ates F, Durmaz MS, et al. Assessment of thyroid gland elasticity with shear-wave elastography in Hashimoto's thyroiditis patients. J Ultrasound 2020; 23; 543-51.
32. Hussein LA, Abdulwahid HM, Kamal AM. The value of ultrasound elastography in diffuse thyroid disease among a sample of Iraqi population. J Med Sci 2021; 9:1647-53.

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Comparison of respiratory tract pathogens and antibiotic susceptibility profiles of patients diagnosed with COVID-19 with pre-COVID-19

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ABSTRACT

Objective: It is aimed to compare the respiratory tract agents and antibiotic resistance rates in patients with a diagnosis of COVID-19 with the non-COVID-19 period.

Material and Method: Patients diagnosed with bacterial respiratory tract infection between March 2019 and March 2021 were included in the study. Bacteria identification and antibiotic susceptibility were evaluated according to automated system and EUCAST standards.

Results: Between March 2019-March 2020 (before the pandemic), the most common bacterium was *Pseudomonas aeruginosa* (*P. aeruginosa*) 280 (15.5%) second *Acinetobacter baumannii* (*A. baumannii*) in a total of 1797 patients hospitalized in the service and intensive care units, and the resistance rates were the same. Between March 2020 and 2021, a total of 1357 COVID -19 patients were found in clinical and intensive care units, and the most common reproducing agent was *A. baumannii* 168 (12.3%), the second *P. aeruginosa* 164, and resistance rates were found to invrease.

Conclusion: The increase in the resistance rates of bacteria causing respiratory tract infection was remarkable. It was determined that *P. aeruginosa* and *A. baumannii*, which were the most common isolates before the pandemic and showed high resistance rates against all antibiotic groups, were the most common bacteria during the pandemic period.

Keywords: Antimicrobial susceptibility; COVID-19; respiratory infection

INTRODUCTION

Co-infection and secondary infections due to severe flu infections are common (1). Coronaviruses are single-stranded, enveloped, positive-sense RNA viruses. There are various subtypes (HKU1-CoV, HcoV-NL63, HCoV-OC43 and HCoV-229E) that can be easily transmitted from person to person. It is a large family of viruses that can cause severe acute respiratory syndrome ("severe acute respiratory syndrome" SARS) and Middle East respiratory syndrome ("Middle East respiratory syndrome" MERS) from a self-limiting mild infection picture that is very common in the community, such as the common cold (2). COVID-19 is a contagious disease that can cause death in rapidly progressing elderly and chronically ill people in the world. It can affect many organs such as the liver, brain, kidney, especially the lungs (3). In the pneumonia epidemic in Wuhan, China in December 2019, the name of the disease identified as SARS CoV-2 was accepted as coronavirus disease 2019 (COVID-19). The source of infection of the disease has not yet been clarified. From the available data, they are considered to be wild animals. Lung is the organ that is most affected and has an effect on mortality. The most common complications in patients with COVID-19 admitted to the hospital were pneumonia (79.1%), ARDS (3.37%), and shock (1%). Apart from these, disseminated intravascular coagulation, acute kidney injury, and rhabdomyolysis were observed less frequently (4). The diagnosis of COVID-19 is made by real-time reverse transcriptase polymerase chain reaction (RT-PCR) test, taken from oropharyngeal and nasopharyngeal swabs. False-negative results may be encountered due to the low sensitivity of the test. For this reason, patients should be evaluated together with clinical, thoracic computed

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tomography (CT) and laboratory findings for the diagnosis (4,5). Lower respiratory tract infections are among the most common hospital-acquired infections in patients hospitalized in intensive care units, and the use of broad-spectrum antibiotics in the treatment has led to the emergence of antibiotic resistance in the agents that cause this type of infection (6). In this study, it was aimed to evaluate the infectious agents and antimicrobial resistance profiles of patients with respiratory tract infection in patients with a diagnosis of COVID-19, and to determine and compare the infectious agents and antimicrobial resistance profiles of patients with respiratory tract infections before the pandemic.

MATERIAL AND METHOD

The study was carried out with the permission of the Fırat University Non-Interventional Research Ethics Committee (Decision No: 2021/04-31 Date: 18.03.2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between March 1, 2020 and March 1, 2021, respiratory tract infection agents and antimicrobial resistance profiles of patients diagnosed with COVID-19 were evaluated by retrospectively comparing the infectious agents and antimicrobial resistance profiles of patients with pre-pandemic respiratory tract infections. In more than one respiratory tract sample belonging to the same patient, only one growth of the same bacteria showing the same antimicrobial susceptibility pattern was evaluated. The first samples of the patients were taken into account and studied. Microbiological analyzes of sputum and DTA samples taken from a total of 3154 adult patients with respiratory tract infection and inpatient treatment, 1797 before the pandemic and 1357 with a diagnosis of COVID-19 were performed and the results were evaluated. Appropriately taken sputum and DTA samples were cultivated according to conventional culture methods and culture plates were incubated for 18-24 hours at 35-37°C in an environment with 5-10% CO2 and growth was evaluated at the end of the incubation. Identification of bacterial isolates was carried out according to the manufacturer's instructions using the automated system Vitek 2 (bioMérieux, France). Antimicrobial susceptibility test was evaluated by Vitek 2 (bioMérieux, France) automated system according to EUCAST (The European committee on antimicrobial susceptibility testing) criteria (7). Colistin resistance for *A. baumannii* species was studied by liquid microdilution method. The rates of the first bacteria isolated as causative agents and the antimicrobial resistance rates of these bacteria were analyzed and compared retrospectively as Pre-Pandemic Period (PPP) and Pandemic Period (PP).

Statistical Analysis

In the study, which was planned as a retrospective cross-sectional study, to reveal the difference between the rates of respiratory tract infection agents and antimicrobial resistance in the pandemic and pre-pandemic period, the difference between the rates of the pre- and post-COVID period was investigated using the Z test for dependent and independent rates. In addition, chi-square and/or Fisher's exact test were used for comparisons between gender and other sociodemographic characteristics. Obtained results were expressed with frequency distributions and percentages and $p<0.05$ value was considered statistically significant. IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp. (IBM Corp. Released 2015) was used for statistical analyzes used in the research.

RESULT

Yeast pathogen was isolated in 61 patients and bacterial pathogen in 818 patients from 626 sputum (34.8%) and 1171 DTA (65.1%) cultures of 1797 patients (1041 males, 756 females) before the pandemic. Of the isolated pathogens, 740 (90.4%) were Gram-negative and 78 (9.5%) were Gram-positive bacteria. *P. aeruginosa* (34.2%), *A. baumannii* (22.2%), *K. pneumoniae* (10.7%), (4.2%) and *E. coli* (3.5%) were most commonly isolated. 15.4% of the detected bacteria are other Gram-negative bacteria (*Stenotrophomonas maltophilia*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Serratia marcescens*, *Providencia rettgeri*, *Citrobacter freundii*). The distribution of bacterial agents detected before the pandemic is given in **Table 1**. During the pandemic period, yeast in 101 patients and bacterial pathogen in 608 patients were isolated from 245 sputum (18%) and 1112 DTA (82%) cultures of 1357 patients (752 men, 605 women). Of the isolated pathogens, 554 (91.1%) were Gram-negative and 54 (8.8%) were Gram-positive bacteria. *A. baumannii* (27.6%), *P. aeruginosa* (27%), *K. pneumoniae* (15%), *E. coli* (4.2%) and *P. putida* (4.1%) were most commonly isolated. 13.15% of the detected bacteria are other Gram-negative bacteria. (*Stenotrophomonas maltophilia*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Serratia marcescens*, *Providencia rettger*, *Citrobacter freundii*) The distribution of bacterial agents detected during the pandemic period is given in **Table 2**.

Microorganisms and antibiotic resistance rates isolated during the Pre-Pandemic Period (PPP) and Pandemic Period (PP) in sputum samples are given in **Table 3**, and the rates of microorganisms and antibiotic resistance isolated during PPP and PP in Aspirate samples are given in **Table 4**. *P. aeruginosa* strains isolated from sputum samples were most sensitive to the antibiotic colistin (COL) (71.2%) during the PPP period, while the antibiotic to which it was most resistant was Amikacin (AK) (69.2%); It

was determined that COL (92.4%) was the most sensitive antibiotic in the PP period and Piperacillin/Tazobactam (PRP) (69.2%) was the most resistant antibiotic. The PPP period of *A. baumannii* strains was the most sensitive antibiotic for COL (100%), the most resistant antibiotic for Meropenem (MEM) (97.5%); It was determined that COL (100%) was the most sensitive antibiotic in the PP period, and Gentamicin (G), AK, CIP (Ciprofloxacin), CAZ (Ceftazidime), IPM (Imipenem), MEM (83.3%) were the most resistant antibiotics. The antibiotic COL, IMP (92.9%) to which *K. pneumoniae* strains are most sensitive during PPP period, while the antibiotic to which they are most resistant is Ampicillin/sulbactam (SAM) (100%); It was determined that the most sensitive antibiotic in the PP period was IMP (71.5%), and the most resistant antibiotic was SAM (100%). The antibiotic to which *E. coli* strains are most sensitive during PPP period is COL, IMP (100%), and the antibiotic to which they are most resistant is SAM (100%); It was determined that COL, IMP, MEM (100%) was the most sensitive antibiotic in the PP period, and SAM (100%) was the most resistant antibiotic. It was determined that the antibiotic COL (63.7%) was the most sensitive of *P. putida* strains during the PPP period, and the antibiotic to which it was most resistant was MEM (90.9%). The most sensitive and most resistant antibiotic distribution of sputum samples according to bacteria is given in **Table 5**. *P. aeruginosa* strains isolated from DTA samples were most sensitive to COL (81.6%) during PPP period, and to PRP (96%); It was determined that COL (93.3%) was the most sensitive antibiotic in the PP period, and PRP (84%) was the most resistant antibiotic. *A. baumannii* strains are most sensitive to COL (89.5%) during PPP, most resistant to antibiotics IMP, MEM, SAM, CAZ, CIP (100%); It was determined that COL (89.5%) was the most sensitive antibiotic in the PP period, and IMP, MEM, SAM, CAZ, CIP (100%) were the most resistant antibiotics. *K. pneumoniae* strains are most sensitive to COL(54%) during PPP, and SAM,CAZ(100%); It was determined that the most sensitive antibiotic in the PP period was IMP (44.1%), and the most resistant antibiotic was SAM (100%). The most sensitive antibiotics of *E. coli* strains during PPP period are MEM and IMP (100%), while the most resistant antibiotics are SAM, CAZ, FEP (100%); It was determined that COL, IMP, MEM (100%) were the most sensitive antibiotics in the PP period, and SAM (100%) was the most resistant antibiotic. The antibiotic COL (70.9%) to which *P. putida* strains are most sensitive during the PPP period, and the antibiotics to which they are most resistant are AK, CAZ, FEP (100%); It was determined that COL (84%) was the most sensitive antibiotic in the PP period, and CAZ, FEP, PTZ (84%) were the most resistant antibiotics. The most sensitive and most resistant antibiotic distribution of DTA samples according to bacteria is given in **Table 6**.

The comparison of bacteria growing in sputum and DTA is given in **Table 7**, and no significant difference was observed between the batteries.

Table 1. Distribution of Commonly Isolated Pathogenic bacteria in Sputum and DTA cultures before the pandemic

Common isolates	Sputum		Deep tracheal Aspirate		Total	
	n	%	n	%	n	%
Pseudomonas aeruginosa	52	18.5	228	81.4	280	45.6
Acinetobacter baumannii	40	22	142	78	182	29.6
Klebsiella pneumoniae	14	16	74	84	88	14.3
Pseudomonas putida	11	31.4	24	68.5	35	5.7
Escherichia coli	18	62	11	38	29	4.7

Table 2. Distribution of Commonly Isolated Pathogenic bacteria in Sputum and DTA cultures during the pandemic period

Common isolates	Sputum		Deep tracheal Aspirate		Total	
	n	%	n	%	n	%
Acinetobacter baumannii	6	3.57	162	96.42	168	35.4
Pseudomonas aeruginosa	13	8	151	92	164	34.5
Klebsiella pneumoniae	7	7.7	84	92.3	91	19.19
Escherichia coli	4	15.38	22	84.61	26	5.48
Pseudomonas putida	-	-	25	100	25	5.27

Table 3. Microorganisms and antibiotic resistance rates isolated in sputum samples during the Pre-pandemic period and the Pandemic period

SPUTUM													
Microorganism	**Period**	**n**	**AMC**	**SAM**	**G**	**AK**	**SXT**	**CİP**	**CAZ**	**FEP**	**PTZ**	**IMP**	**MEM**	**COL**
A. baumannii	PPP	40	-	87.5	87.5	87.5	90	95	95	-	-	85	97.5	0
A. baumannii	PP	6	-	66.6	83.3	83.3	50	83.3	83.3	-	-	83.3	83.3	0
p			NA	0.4718	0.7151	0.7151	0.0531	0.8448	0.8448	NA	NA	0.6162	0.6053	NA
P. aeruginosa	PPP	52	-	-	61.5	69.2	-	61.5	61.5	50	63.4	48	50	28.8
P. aeruginosa	PP	13	-	-	15.3	30.7	-	61.5	53.8	30.7	53.8	61.5	53.8	7.6
p			NA	NA	0.0075	0.0256	NA	0.7500	0.8490	0.3485	0.7508	0.5750	0.9482	0.2194
K. pneumoniae	PPP	14	78.5	100	35.7	35.7	78.5	57.1	85.7	85.7	71.4	7.1	50	7.1
K. pneumoniae	PP	7	71.4	100	28.5	28.5	71.4	85.7	85.7	57.1	71.4	28.5	71.4	28.5
p			0.8425	NA	0.8720	0.8720	0.8547	0.4125	0.5085	0.3645	0.6085	0.5088	0.6409	0.5088
E. coli	PPP	18	66.6	100	44.4	27.7	44.4	77.7	83.3	72.2	33.3	0	5.5	0
E. coli	PP	4	75	100	25	25	25	75	75	50	25	0	0	0
p			0.7895	NA	0.8794	0.6092	8794	0.5875	0.7436	0.7881	0.7863	NA	0.3935	NA
P. putida	PPP	11	-	-	63.6	72.7	-	81.8	81.8	81.8	81.8	72.7	90.9	36.3
P. putida	PP	-	-	-	-	-	-	-	-	-	-	-	-	-
p														

AMC: Amoxicillin/clavulanic acid, SAM: Ampicillin sulbactam, CN: Gentamycin, AK: Amikasin, SXT: Sulfamethoxazole/Trimethoprim, CIP:Ciprofloxacin, CAZ: Ceftazidime, FEP: Cepepim, TPZ: Piperacillin/Tazobactam, IPM: imipenem, MEM: Meropenem COL: Colistin

Table 4. Microorganisms and antibiotic resistance rates isolated in DTA samples during the Pre-pandemic period and the Pandemic period

Microorganism	Period	n	AMC	SAM	G	AK	SXT	CİP	CAZ	FEP	PTZ	IMP	MEM	COL
A. baumannii	PPP	142		100	82.3	98.5	83.8	100	100	-	-	100	100	10.5
A. baumannii	PP	162		100	90.7	95	93.8	100	100	-	-	100	100	9.2
P			NA	NA	0.0469	0.1708	0.0091	NA	NA	NA	NA	NA	NA	0.8517
P. aeruginosa	PPP	228	-	-	75	67.5	-	63.1	60	73.6	96	80.7	85	18.4
P. aeruginosa	PP	151	-	-	51.6	51	-	61	49.6	58.2	84	74.8	66.8	6.62
P			NA	NA	<0.001	0.0018	NA	0.7606	0.0587	0.0025	0.001	0.2157	0.001	0.0019
K. pneumoniae	PPP	74	85.1	100	78.3	71.6	94	90.5	100	94.5	81.08	68.9	93.3	46
K. pneumoniae	PP	84	85.7	100	63.1	57.1	83.3	90.4	89.2	94	79.4	55.9	61.9	79.7
P			0.9051	NA	0.0561	0.0841	0.0657	0.8027	0.0102	0.8357	0.9487	0.1296	<0.001	<0.001
E. coli	PPP	11	36.3	100	81.8	-	72.7	72.7	100	100	36.3	0	0	18.8
E. coli	PP	22	50	100	50	-	63.6	77.2	77.2	77.2	40.9	0	0	0
P			0.7082	NA	0.1662	NA	0.8957	0.8836	0.2280	0.2280	0.9021	NA	NA	0.1806
P. putida	PPP	24	-	-	80	100	-	95.8	100	100	95.8	95.8	95.8	29.1
P. putida	PP	25	-	-	79.1	80	-	80	84	84	84	80	80	16
P			NA	NA	0.7824	0.0658	NA	0.2113	0.1278	0.1278	0.3727	0.2113	0.2113	0.4493

AMC: Amoxicillin/clavulanic acid, SAM: Ampicillin sulbactam, CN: Gentamycin, AK: Amikasin, SXT: Sulfamethoxazole/Trimethoprim, CIP:Ciprofloxacin, CAZ: Ceftazidime, FEP: Cepepim, TPZ: Piperacillin/Tazobactam, IPM: imipenem, MEM: Meropenem COL: Colistin

Table 5. Distribution of sputum samples to which they are most susceptible and most resistant to bacteria

Microorganism	Period	Most Sensitive	%	Most Resistant	%
A. baumannii	ppp	COL	100	MEM	97.5
A. baumannii	pp	COL	100	G/AK/CİP/CAZ/IPM/MEM	83.3
P. aeruginosa	ppp	COL	71.2	AK	69.2
P. aeruginosa	pp	COL	92.4	CİP,IMP	61.5
K. pneumoniae	ppp	COL/IMP	92.9	SAM	100
K. pneumoniae	PP	IMP	71.5	SAM	100
E. coli	ppp	COL/IMP	100	SAM	100
E. coli	pp	COL/IMP/MEM	100	SAM	100
P. putida	ppp	COL	63.7	MEM	90.9
P. putida	pp	-		-	-

Table 6. Distribution of DTA samples to which they are most sensitive and resistant to bacteria

Microorganism	Period	Most Sensitive	%	Most Resistant	%
A. baumannii	ppp	COL	89.5	SAM/CİP/CAZ/IPM/MEM	100
A. baumannii	pp	COL	90.8	SAM/CİP/CAZ/IPM/MEM	100
P. aeruginosa	ppp	COL	81.6	PTZ	96
P. aeruginosa	pp	COL	93.3	PTZ	84
K. pneumoniae	ppp	COL	54	SAM/CAZ	100
K. pneumoniae	pp	IMP	44.1	SAM	100
E. coli	ppp	IMP/MEM	100	SAM/CAZ/FEP	100
E. coli	pp	IMP/MEM/COL	100	SAM	100
P. putida	ppp	COL	70.9	AK/CAZ/FEP	100
P. putida	pp	COL	84	CAZ/FEP/PTZ	84

Table 7. Comparison of bacteria growing in sputum and DTA

Bacterium	Sputum [Pre-Post] p value	DTA [Pre-Post] p value
Pseudomonas aeruginosa	0.0039	0.0037
Acinetobacter baumannii	<0.0001	<0.0001
Klebsiella pneumoniae	0.1362	0.1370
Escherichia coli	0.0012	0.0012
Pseudomonas putida	0.0058	0.0056

DISCUSSION

The COVID-19 pandemic is a viral pneumonia pandemic. Interpersonal transmission occurs through direct contact or through droplets spread by sneezing or coughing from an infected person. The most common initial symptoms in patients found to be infected with COVID-19 are cough, fever, and fatigue. Other symptoms and signs are headache, hemoptysis,

diarrhea, sputum, dyspnea and lymphopenia (8). Although the clinical course of people infected with COVID-19 is mild at a rate of 81%, 14% require severe care and 5% require intensive care (9). In the elderly, the mortality rate between the ages of 70 and 79 is 8 percent, and the mortality rate at the age of 80 and above is 14.8% (10). Zhou et al. reported that in the current coronavirus disease 2019 (COVID-19) pandemic, 50% of COVID-19 patients who died had secondary bacterial infections (11). In a systematic review of eleven case series, including 2002 patients, it was found that the risk of severe disease is quadrupled in patients with COVID-19 accompanied by COPD, and this risk is approximately doubled in active smokers; In addition, it was found that the need for intensive care, mechanical ventilation and mortality were statistically significantly higher in patients with COPD (12).

Opportunistic pathogens reproduce especially in respiratory tract samples and have intense antibiotic resistance (13). Although the distribution of ventilator-associated pneumonia (VAP) factors varies according to regions, as in other nosocomial infections, Gram-negative bacteria such as *K. pneumoniae*, *P. aeruginosa*, *A. baumannii* are mostly isolated. However, in recent years, it has been observed that Gram-positive agents, especially *S. aureus*, have increased gradually (14). Clark D Russell et al found *S. aureus* and *Haemophilus influenzae* as the most common secondary respiratory tract infections in patients diagnosed with COVID-19, and Enterobacter spp. and *S. aureus* as coinfection agents (15). In the study of Koçak et al. 641 bacteria considered pathogenic were isolated from 245 sputum and 396 DTA cultures taken from 442 patients in total. The most commonly isolated agents are *A. baumannii* (25%), *P. aeruginosa* (12.6%), Klebsiella spp (14.7%), *E. coli* (10%), *H. influenzae* (6.9%), *S. aureus* (5.5%)) and *Streptococcus pneumoniae* (5.1%) (16). From the Bronchoalveolar lavage (BAL) cultures of 13 COVID-19 patients who were followed up intubated in the study of Araç E. et al.; They detected *K. pneumoniae* in five (55.5%), *A. baumannii* in one (11.1%), *E. coli* in one (11.1%), *P. aeruginosa* in one (11.1%) and *Burkholderia cepacia* in one (11.1%)(17). In our study, the most common bacterial agents before the pandemic; *P. aeruginosa* 280(15.5%), *A. baumannii* 182(10.1%), *K. pneumoniae* 88(4.89%), *P. putida* 35(1.9%), *E. coli* 29(%) 1.6). During the pandemic period, the most common *A. baumannii* 168 (12.3%), *P. aeruginosa* 164 (12%), *K. pneumoniae* 91 (6.7%), *E. coli* 26 (1.9%), *P. putida* 25 (1.8%). Gazi et al. examined the lower respiratory tract samples of 835 intensive care patients and reported that antibiotic resistance rates in Pseudomonas and A. baumanni species were higher than isolates isolated from other services (18). In our study, aspirate samples before and during the Pandemic period increase the resistance rate in all isolated bacteria compared to sputum samples. In the aspirate samples, the resistance rates of *A. baumannii* to G, SXT increased during the PP. The resistance rate of *P. aeruginosa* to G, AK, FEP, PTZ, MEM, COL decreased during the pandemic period, and the resistance rate to CAZ, MEM, COL during the pandemic period of *K. pneumoniae* decreased. In sputum samples, the resistance rate of *P. aeruginosa* decreased in G and AK during the pandemic period.

Carbapenems are known as the most effective beta-lactam antibiotics against bacterial resistance (19). Carbapenems are mostly used in the empirical treatment of serious bacterial infections (20). According to the research in Europe in the 2007 MYSTIC program; It has been reported that the most effective antibacterial group against nonfermentative gram-negative bacteria is carbapenems, but there is an increase in Acinetobacter strains which showing multi-antibiotic resistance and Pseudomonas strains which showing imipenem-resistance (21). Baumgart et al., in their study, found carbapenem resistance in Acinetobacter species to be 80% (22).In our study, carbapenem resistance in sputum samples was 83.3%-97.5% for *A. baumannii*, 48-61.5% for *P. aeruginosa*, 7.1-71.4% for *K. pneumoniae*, 0-5.5% for *E. coli*, and 72.7-90.9% for *P. putida*. Carbapenem resistance in our aspirate samples was 100% for *A. baumannii*, 66.8-85% for *P. aeruginosa*, 55.9-93.3% for *K. pneumoniae*, 0% for *E. coli* and 80% for *P. putida*.

Colistin resistance occurs especially in people who take colistin therapy for a long time. Its combination with other antimicrobials is the most commonly used option in empirical treatment (23). In a multicenter study conducted in Southern Europe (Italy, Greece and Spain), the colistin resistance of *A. baumannii* strains obtained from respiratory samples of patients with VAP was reported to be 47.7% (24). In our study, colistin resistance for *A. baumannii* was 0% in PPP and PP period in sputum samples and 10.5% in PPP period in Aspirate samples. 9.2% in the PP period. The emergence of multidrug-resistant and carbapenem-resistant *P. putida* has become a cause for concern. Carbapenem-resistant *P. putida* and *P. aeruginosa* isolates are increasingly reported in areas other than tracheal aspiration, urinary system and blood (25,26). The fact that it was seen among the most frequently isolated bacteria in our study and that it showed serious antimicrobial resistance signals that it will cause important problems in the future. In addition, increased yeast growth due to intensive antibiotic use and duration of hospitalization (27), which has been shown in various studies, also increased in our study.

CONCLUSION

Respiratory tract infections are the second most common cause of death worldwide. The use of broad-spectrum antibiotics causes the development of much more resistant strains in the respiratory tract. We think that if each hospital determines the microorganisms isolated in their own laboratory and their antimicrobial resistance patterns at regular intervals, shares these data with the relevant clinics and determines the appropriate empirical treatment choices, it can be effective in the control of nosocomial infections.

In addition, off-label use of antibiotics in COVID-19 infections has increased antibiotic resistance and accelerated the development of fungal infections.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Fırat University Non-Interventional Research Ethics Committee (Decision No: 2021/04-31 Date: 18.03.2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Viruses 2016; 10: 394–403.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.
3. Cao Y, Liu X, Xiong L, Cai K. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis. J Med Virol 2020; 10.1002/jmv.25822.
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med 2020; 382: 1708-20.
5. Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol 2020; 92: 1518-24.
6. Claeys KC, Zasowski EJ, Trinh TD, Lagnf AM, Davis SL, Rybak MJ. Antimicrobial stewardship opportunities incritically ill patients with gram-negative lowerrespiratory tract infections: A multicenter crosssectionalanalysis. Infect Dis Ther 2018; 7: 135-46.
7. EUCAST 2019. The European committee on antimicrobial susceptibility testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. http: //www.eucast.org .
8. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020; 109: 102433.
9. Team NCPERE. Vital surveillances: The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) - China. China CDC Weekly 2020; 2: 113-22.
10. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239-42.
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-62.
12. Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis. J Med Virol 2020; 92: 1915-21.
13. Bahceci I. Distribution and antimicrobial susceptibility of *Stenotrophomonas maltophilia* strains isolated from various clinical specimens: an 8-year study. Dicle Med J 2021; 48: 147-52.
14. Gedikli MA, Tuzun B, Sayin K, Ataseven H. Determination of inhibitor activity of drugs against the COVID-19. Bratisl Med J 2021; 122: 497-506.
15. Rusell C, Fairfield C, Drake T, Turtle L, Seaton R. Wootton D Co-infections, secondary infectios, an antimicrobal use in patients hospitalised with COVID-19 during the first pandemic wave from the ısarıc who ccp-uk study: a multicentre, prospective cohort study Lancet Microbe 2021 June 2, 2021
16. Jalali Y, Sturdik I, Jalali M, Payer J. Isolated carbapenem resistant bacteria, their multidrug resistant profile, percentage of healthcare associated infection and associated mortality, in hospitalized patients in a University Hospital in Bratislava. Bratisl Med J 2021; 122: 379-85.
17. E Araç, M Doğan, FE Taşbent, B Feyzioğlu Secondary bacterial infection rates in patients diagnosed with COVID-19. COVID-19 online-international-multidisciplinary symposium, 26-28 June 2020.
18. Gazi H, Ecemis T, Kurutepe S, Gürsev N, Driveoğlu S. Antimicrobial resistance in gram-negative bacteria isolated from lower respiratory tract samples of hospitalized patients. KLIMIK J 2011; 24: 112-5.
19. Agarwal S, Kakati B, Khanduri S, Gupta S. Emergence of carbapenem resistant non-fermenting gram-negative bacilli isolated in an ICU of a tertiary care hospital. J Clin Diagn Res 2017; 11: 4-7.
20. MalekzadeganY, Abdi A, Heidari H, Moradi M, Rastegar E, Saraie HSE. In vitro activities of colistin, imipenem and ceftazidime against drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* isolates in the south of Iran. BMC Res Notes 2019; 12: 301.
21. Turner PJ. MYSTIC Europe 2007: Activity of meropenem and other broad-spectrum agents against nosocomial isolates. Diagn Microbiol Infect Dis 2009; 63: 217-22.
22. Baumgart AMK, Molinari MA, Silveira AC. Prevalence of carbapenem resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in high complexity hospital. Braz J Infect Dis 2010; 14: 433-6.
23. Amaya Villar R, Garnacho Montero J. How should we treat acinetobacter pneumonia? Curr Opin Crit Care 2019; 25: 465-72.
24. Nowak J, Zander E, Stefanik D, et al. High incidence of pandrug-resistant *Acinetobacter baumannii* isolates collected from patients with ventilatorassociated pneumonia in Greece, Italy and Spain as part of the MagicBullet clinical trial. J Antimicrob Chemother 2017; 72: 3277-82.

25. Bogaerts P, Huang TD, Rodriguez-Villalobos H, et al. Nosocomial infections caused by multidrug-resistant *Pseudomonas putida* isolates producing VIM-2 and VIM-4 metallo-beta-lactamases. J Antimicrob Chemother 2008; 61: 749–51.
26. Bahceci İ. Microorganisms that reproduce in wound cultures in Rize region and their antimicrobial susceptibility. Middle Black Sea J Health Sci 2020; 6: 358-68.
27. Batcık S, Bahceci I, Kazancıoglu L, Kazdal H, Ozcan M. Candida species and antifungal susceptibility isolated in intensive care units: a three-year study. Van Med J 2021; 28: 459-65.

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The effect of colchicine treatment on complete blood cell count-based parameters in patients with Behçet's disease

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ABSTRACT

Aim: Behçet's disease (BD) is a systemic disease, with still unknown etiology and pathogenesis and varying disease presentations, characterized by recurrent oral aphthae, followed by genital ulcers, arthritis, variable skin and ocular lesions, gastrointestinal and central nervous system involvement, as well as, vascular disease. Colchicine is one of the oldest remedies still in use today. The study aimed to investigate the effect of colchicine on levels of the complete blood cell count-based parameters in BD.

Material and Method: A total of 117 (participants 60 healthy control and 57 patients with BD) were recruited from the rheumatology department in a single-center case-control study. The laboratory data were obtained from the electronic registration database. Laboratory findings of patients and healthy controls were evaluated. In addition, patients with BD were evaluated for these parameters before colchicine therapy and after 3-month from the beginning of colchicine treatment.

Results: The levels of inflammatory markers such as neutrophil count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and systemic immune-inflammation index (SII), significantly higher than the control group before treatment, decreased to similar levels with the control group in the third month of colchicine use. However, red blood cell distribution width (RDW), mean platelet volume (MPV), and plateletcrit (PCT) were still statistically significantly different from the control group in BD patients.

Conclusion: SII, CRP, ESR, and NLR are useful parameters to evaluate the colchicine response of patients with mucocutaneous BD.

Keywords: Behçet's disease, colchicine, neutrophil to lymphocyte ratio, plateletcrit, systemic immune-inflammation index

INTRODUCTION

Behçet's disease (BD) is a variable vessel vasculitis with multi-system involvement that shows significant heterogeneity among patients regarding demographic features, organ manifestations, frequency and severity of relapses, disease course, response to treatment, and prognosis. Although BD is more common in "Silk Road" populations, it has a universal distribution (1). The interplay between a complex genetic background and both innate and adaptive immune systems is related to the BD clinical features (2). The well-known genetic association is with HLA-B51 (60%). It may start with mucocutaneous findings such as recurrent aphthous stomatitis and genital ulcer and convert a systemic form characterized by ocular, cardiovascular, articular, neurological and gastrointestinal symptoms. Mucocutaneous manifestations decrease the health-related quality of life, whereas major organ involvement may result in severe morbidity/mortality. The symptoms and severity of BD may vary between patients and may change over time in the same patient. Due to the lack of a universally recognized pathognomonic laboratory test, the diagnosis is based on clinical criteria (3, 4). The primary treatment goals are improved health-related quality of life, maintenance of disease remission, and prevention of organ damage. Colchicine is one of the oldest remedies still in use today (5). Many studies have been conducted on tests that may reflect disease activation, be helpful in monitoring treatment efficiency, or predict potential complications of BD. However, there is still a demand for new laboratory markers in patients with BD. Complete blood cell count parameters (CBC) have recently emerged as

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valuable biomarkers of many inflammatory diseases because of their availability and affordability. Pre-treatment CBC-based biomarkers have been reported to reflect systemic and local inflammation associated with cancer progression and prognosis inflammation and oxidative stress in chronic inflammatory and autoimmune diseases (6-9). We aimed to investigate the dynamic changes in hemogram parameters before and after colchicine treatment in BD patients and investigate the anti-inflammatory effect of colchicine on these parameters and their value for BD.

MATERIAL AND METHOD

This study was approved by the Selçuk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 2021/295). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent forms were taken from all participants before the study.

Study Population and Design

We selected 57 new patients with mucocutaneous BD at diagnosis. BD diagnosis was made according to The International Study Group (ISG) criteria. The ISG criteria for BD require oral aphthous ulcers and two or more additional manifestations: genital aphthous ulceration, eye lesions (uveitis, retinitis), skin lesions (folliculitis, papulopustular lesions, acneiform nodules, erythema nodosum) and/or a positive pathergy test (3). All BD patients were selected from patients who were administered only colchicine (1,5 mg /day)

The study's inclusion criteria were being 18 years old or above and not receiving any systemic treatment for BD at the time of hospital application. Healthy controls were selected from patients admitted to the outpatient checkup clinic without any known diseases. Pregnant or breastfeeding women, smoking, alcohol, oral contraceptive use, concomitant obesity (BMI >30 kg/m2), hypertension, diabetes mellitus, endocrine disorders, malignancies, acute or chronic infection, chronic haematologic disease, other autoimmune or autoinflammatory diseases, tuberculosis, heart and lung disease, major organ involvement (eye, brain, major intestinal, lung, and cardiovascular involvement) were excluded from the study. Patients' demographic characteristics (gender, age, age of disease onset, duration of illness), mucocutaneous involvement such as oral ulcer, genital ulcer, erythema nodosum and folliculitis, joint involvement, features, and clinical symptoms, physical examination findings, pathergy reaction, laboratory findings, imaging tests and treatment information received were evaluated.

Laboratory Measurements

Hemoglobin, RDW (normal 11%-15%), MPV (normal 7.5-11.5 FL), PCT (%), platelet (K/μL), lymphocyte (K/μL), neutrophil (K/μL) and monocytes (K/μL) levels were determined using an automatic blood counting system for each participant. NLR, MLR, and PLR were calculated using the ratio of neutrophil, monocyte, and platelet counts to lymphocyte counts, respectively. Systemic Immune-Inflammation Index (SII) was calculated by the formula: neutrophil (Neu) x platelet (Plt) / lymphocyte (Lym). Also, the erythrocyte sedimentation rate (ESR; normal 0-20 mm/hour) and C-reactive protein (CRP; normal 0-8 mg/L) were recorded. Patients with BD were evaluated for these parameters before colchicine therapy and after 3-month from the beginning of colchicine treatment.

Statistical Analysis

All data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 21.0. The normality distribution of scale variables was checked using the Shapiro-Wilk test. Data were expressed mean±standard deviation. Wilcoxon test was used for dependent samples. Independent samples were compared with the Mann-Whitney U test. Pearson's chi-square test was used for categorical variables. ESR, CRP, and SII values were compared with Spearman's correlation test and presented with a simple scatterplot. Two-sided p-values less than 0.05 were considered statistically significant.

RESULTS

Demographic and clinical characteristics of the BD and control groups included in the study were as in **Table 1**. The groups were identical in terms of age and gender (p=0.061, p=0.603; respectively). There was no statistical difference between the control and BD groups regarding BMI and smoking (p=0.167, p=0.404; respectively). In **Table 2**, statistical differences between BD patients whose hemogram parameters were evaluated before and after treatment and healthy controls were analyzed separately. The decrease in NLR value was statistically significant (p3<0.001). There was no significant change in hemoglobin and platelet levels (p3=0.744, p3=1.000; respectively). Although the decrease in MPV values after treatment was not statistically significant, a significant decrease was observed in PCT levels (p3=0.237, p3=0.006; respectively). There was a significant decrease in inflammatory markers such as ESR and CRP (both, p3<0.001). Similarly, a significant decrease was observed in the SII value (p3=0.003). The SII calculation parameters, neutrophil, lymphocyte, and platelet counts, might already be expected to correlate with SII. Therefore, correlation analyzes of SII with

only CRP and ESR were performed. It was determined that SII had moderate correlations with CRP and high correlations with ESR (r=0.466, p<0.001, r=0.698, p<0.001; respectively) (**Figure 1**).

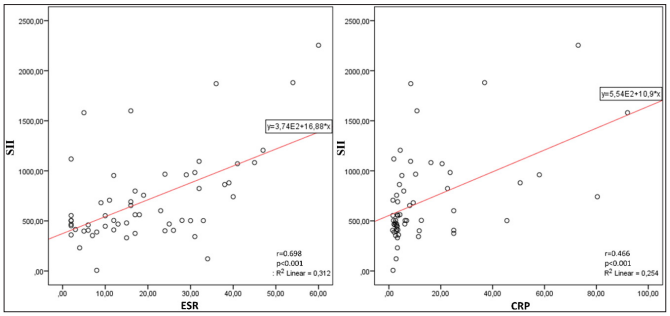

Figure 1. Positive correlation of SII with ESR and CRP
SII: Systemic immune-inflammation index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Table 1. Presentation of demographic and clinical features

	Healthy control (n=60)	Behçet's disease (n=57)	p value
Age (years)	30.5±4.8	32.2±6.8	0.061*
Sex			0.603
Man	26 (43.3%)	22 (38.6%)	
Woman	34 (56.7%)	35 (61.4%)	
BMI (kg/m2)	22.9±3.6	22.1±2.5	0.167*
Clinical features			
Oral aphthae	-	57 (100.0%)	-
Genital ulcer	-	15 (26.3 %)	-
Erythema nodosum	-	17 (29.8 %)	-
Folliculitis	-	26 (45.6%)	-
Arthralgia	-	36 (63.1%)	-
Pathergy positivity	-	37 (64.9%)	-

BMI – body mass index; N/A – not applicable
Data were expressed as mean±standard deviation—Mann-Whitney U (*) and Pearson's chi-square tests were used.

The levels of inflammatory markers such as neutrophil count, NLR, CRP, ESR, and SII, significantly higher than the control group before treatment, decreased to similar levels with the control group in the third month of colchicine use. However, values such as RDW, MPV, and PCT were still statistically significantly different from the control group in patients with BD despite treatment (**Table 2**).

DISCUSSION

Endothelial injury has been proposed as one of the main pathophysiological mechanisms underlying the BD, promoting a hyperinflammatory and prothrombotic state leading to worse clinical outcomes. The activated neutrophils may be involved in the process of tissue damage in BD. It has been recently shown that neutrophil activation promotes fibrinogen oxidation, thrombosis formation, reactive oxygen species (ROS) generation and sustains BD activity (2). Growing data suggest that neutrophils can contribute to thrombo-inflammation via ROS and through additional mechanisms, including the release of neutrophil extracellular traps (NETs) (10). According to evidence-based medicine, colchicine is a first-line effective therapy in BD's mucosal, cutaneous, pleuropericardial, and abdominal complications. Neutrophil function, which is essential in the pathogenesis of the disease, is modified by this drug. It is believed to suppress the secretion of cytokines, chemokines, and in vitro platelet aggregation by disrupting the cytoskeleton (5). Moreover, studies show that colchicine, despite the lack of an anti-oxidant power, exerts a protective effect on oxidation-induced NETs production and oxidation-

Table 2. Comparison of hemogram parameters before and after colchicine treatment in Behçet's disease separately with the healthy control group

Parameters	A (n=57) BD, pre-treatment 0th month	B (n=60) Healthy control	C (n=57) BD, post-treatment 3rd month	p1-value (A vs. B)	p2-value (B vs. C)	p3-value (A vs. C)
Hemoglobin (g/dl)	13.9±1.5	14.4±1.3	14.0±1.5	0.064	0.215	0.744
MCV (fl)	83.9±5.5	85.1±3.7	84.4±5.7	0.307	0.993	0.174
RDW (%)	14.4±1.7	12.9±1.0	14.1±1.6	<0.001	<0.001	0.995
Neutrophil (10^6/l)	5004±1882	4261±1690	4402±1462	0.012	0.367	0.018
Lymphocyte (10^6/l)	2143±533	2915±602	2297±687	0.266	0.872	0.153
Monocytes (10^6/l)	567±193	542±150	591±189	0.627	0.093	0.264
Platelet (10^9/l)	277±80	271±62	273±69	0.409	0.643	1.000
PCT (%)	0.24 ±0.06	0.28±0.06	0.22±0.05	0.003	<0.001	0.006
MPV (fl)	8.45±1.21	10.2±1.2	8.14±1.19	<0.001	<0.001	0.237
NLR (10^{-2})	251±137	194±76	207±96	0.010	0.593	<0.001
MLR (10^{-2})	28±12	24±7	28±14	0.330	0.252	1.000
PLR	136.5±49.9	124.7±35.6	130.7±68.7	0.168	0.737	0.141
CRP (mg/l)	14.0±20.5	3.8±2.1	4.8±5.0	0.003	0.478	<0.001
ESR (mm/hour)	19.7±14.6	10.3±8.6	10.4±8.0	0.002	0.823	<0.001
SII	706±442	532±250	556±251	0.041	0.624	0.003

Data were expressed as mean±standard deviation. Mann-Whitney U test was used. Significant values were shown in bold.
BD: Behçet's disease; MCV: Mean corpuscular volume; RDW: Red cell distribution width; PDW: Platelet distribution width; PCT: Plateletcrit; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte ratio; MLR: Monocytes/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SII: Systemic immune-inflammation index

induced neutrophil apoptosis (11). Simple markers are needed for diagnosis, follow-up treatment plan, and prognosis for BD. Cellular components of blood and their ratios may give insight into the extent of ongoing inflammation. In recent years, there has been a trend in clinical practice to utilize inflammation-based indexes as assessment tools for disease activity of various kinds of inflammatory diseases and prognostic indicators in the survival of patients with malignant tumors (6-9). Furthermore, SII may be a potentially helpful index in clinical practice to follow-up and manage these patients by monitoring response to anti-inflammatory treatment modalities. The following study investigates whether hematologic parameters such as SII, NLR, RDW, MPV, and PCT are associated with colchicine efficacy in BD. It has been reported in some studies that the NLR, PLR, and RDW are significantly higher in BD patients than in the healthy group, suggesting their value as promising inflammatory biomarkers in BD (12-20). Several studies observed the significant association of NLR with BD activity. In addition, Ünlü et al. (21) reported that high NLR might be associated with endothelial dysfunction and reflect BD activity. In our study, there was a statistically significant difference between BD patients in terms of NLR, which was higher than the control group. In addition, NLR decreased in these treated patients. NLR may serve as a surrogate assay for BD response to colchicine. Djaballah-Ider et al. (16) found results similar to this study, but the patient group was under colchicine + steroid treatment, not just those under colchicine treatment. The SII, a novel inflammation-based biomarker, integrates neutrophils, platelets and lymphocytes. SII covers NLR and platelets and is calculated by the formula platelet x NLR. One of the most outstanding findings of our study was the demonstration of the positive correlation of SII with CRP and ESR. According to previous studies, SII may have a high prognostic value in cancer patients, and an elevated pre-treatment SII is associated with poor outcomes in cancer patients (9). SII is a valuable biomarker of the inflammatory status and immune response. Recently, studies have also reported using SII as an indicator for autoimmune diseases, such as an index to assess the disease activity of patients with BD or to predict the poor prognosis of antineutrophil cytoplasmic antibody-associated vasculitis (22-24). Recently, the diagnostic utility of SII has been studied in autoimmune diseases, such as adult-onset Still's disease (25). Our results showed that the SII levels in BD patients were higher than those of healthy controls and decreased in these treated patients. SII changes could predict these patients' responses to treatment and clinical outcomes. Platelets play an essential role in the integrity of normal hemostasis; MPV is the indicator of platelets' function. Changes in the MPV in many different conditions have been researched. While the MPV was not found to be associated with disease and/or disease activity in some of these conditions, it is increased or decreased in others. An increased MPV has been associated with an increased thrombotic disposition (26, 27). A higher MPV in patients with active BD has also been reported (28). Ataş et al. (11) evaluated the effect of colchicine on MPV levels, and after colchicine treatment, a decrease in MPV was obtained in their study. This study found the MPV level higher in BD patients than in healthy controls, but the difference persisted regardless of whether it changed significantly with colchicine. There was no significant difference in MPV levels among the patients with BD and healthy controls in some studies. An explanation for this discrepancy was the possibility that MPV alone was not an appropriate indicator of platelet activation following a conclusion stated. MPV reflects early platelet activation and PCT obtained by multiplying platelet with MPV, the percentage of blood volume occupied by platelets. According to recent studies, PCT provides more comprehensive data on total platelet mass and is expected to be a tumor-related biomarker (29, 30). An increased PCT has been found to be associated with an increased risk of coronary artery disease and venous thrombosis (29, 30). PCT may also be a good indicator of inflammation. A recent study found a higher PCT value than the healthy control (31). Thrombocytes play an essential role in various inflammatory disorders by activating immune cells and stimulating immune responses, consistent with the current study findings of significantly high MPV and PCT values in BD (26, 31, 32). RDW is another recommended parameter related to inflammatory processes. In several recent studies, a significant increase has been reported in RDW in patients with a history of BD, independent of disease activity and involvement characteristics (7, 15). Masoumi et al. (28) determined significantly higher RDW in BD patients with ocular and oral symptoms, independent of disease activity. In a study by Aksoy et al. (15), RDW was significantly higher in BD patients than in a control group and those with active disease compared with inactive disease and the control group. Elevated RDW has also been shown to be an important marker of oxidative stress and inflammation. Several studies have demonstrated an oxidative response in patients with BD; because of the exposure to oxidative stress, the lifetime of erythrocytes decreases, reticulocyte production increases and RDW increases in peripheral blood. RDW, MPV, and PCT are different in BD patients from the control group despite treatment, regardless of whether they changed significantly with colchicine. Although NLR, ESR, CRP, neutrophil count, and SII were different from the pre-treatment healthy control, they were at

the same level as the healthy control post-treatment. SII and NLR were found to be lower in patients with BD after a three-month colchicine treatment as compared with their levels before treatment. We also observed a decrease in inflammatory predictors such as CRP and ESR. A decrease in these parameters supported the anti-inflammatory effect of colchicine. Moreover, any other medicine which affected these parameters was not added to treatment. Therefore it is appropriate to follow up these parameters in patients receiving colchicine.

Several limitations of our study need to be addressed. The sample size was relatively small, and only BD patients wıth mucocutaneous involvement were included in the study. Although the results have provided some evidence of the applicability of NLR and SII, further research is needed to validate these parameters and assess their value as tools for follow-up and evaluate the effect of colchicine on mucocutaneous involvement in BD.

CONCLUSION

SII, CRP, ESR, and NLR are useful parameters to evaluate the colchicine response of patients with mucocutaneous BD.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Selçuk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 2021/295).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

REFERENCES

1. Kiafar M, Faezi ST, Kasaeian A, et al. Diagnosis of Behcet's disease: clinical characteristics, diagnostic criteria, and differential diagnoses. BMC Rheumatol 2021; 5: 2.
2. Mattioli I, Bettiol A, Saruhan-Direskeneli G, Direskeneli H, Emmi G. Pathogenesis of Behçet's syndrome: genetic, environmental and immunological factors. Front Med (Lausanne) 2021; 8: 713052.
3. Criteria for diagnosis of Behçet's disease. International study group for Behçet's disease. Lancet 1990; 335: 1078-80.
4. Chen J, Yao X. A contemporary review of Behcet's syndrome. Clin Rev Allergy Immunol 2021; 61: 363-76.
5. Gasparyan AY, Ayvazyan L, Yessirkepov M, Kitas GD. Colchicine as an anti-inflammatory and cardioprotective agent. Expert Opin Drug Metab Toxicol 2015; 11: 1781–94.
6. Tezcan D, Körez MK, Gülcemal S, Hakbilen S, Akdağ T, Yılmaz S. Evaluation of diagnostic performance of hematological parameters in Behçet's disease. Int J Clin Pract 2021; 10: e14638.
7. Gheita TA, Sakr BR, Rabea RE, Abd ElHamid SM. Value of hematological indices versus VEGF as biomarkers of activity in Behçet's disease. Clin Rheumatol 2019; 38: 2201-10.
8. Wu J, Yan L, Chai K. Systemic immune-inflammation index is associated with disease activity in patients with ankylosing spondylitis. J Clin Lab Anal 2021; 35: e23964.
9. Fest J, Ruiter R, Mulder M, et al. The systemic immune-inflammation index is associated with an increased risk of incident cancer-a population-based cohort study. Int J Cancer 2020; 146: 692-8.
10. Safi R, Kallas R, Bardawil T, et al. Neutrophils contribute to vasculitis by increased release of neutrophil extracellular traps in Behçet's disease. J Dermatol Sci 2018; 92: 143–50.
11. Ataş H, Cemil BC, Canpolat F, Gönül M. The effect of colchicine on mean platelet volume in Behcet's disease. Ann Clin Lab Sci 2015; 45: 545-9.
12. Yolbas S, Yildirim A, Gozel N, Uz B, Koca SS. Hematological ındices may be useful in the diagnosis of systemic lupus erythematosus and in determining disease activity in Behçet's disease. Med Princ Pract 2016; 25: 510-6.
13. Erden F, Karagoz H, Avci A, et al. Which one is best? Platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, or both in determining deep venous thrombosis in Behcet's disease? Biomed Res-India 2017; 28: 5304-9.
14. Lee YH, Song GG. Neutrophil-to-lymphocyte ratio, mean platelet volume, and platelet-to-lymphocyte ratio in Behçet's disease and their correlation with disease activity: ameta-analysis. Int J Rheum Dis 2018; 21: 2180-7.
15. Aksoy ŞN, Savaş E, Sucu M, Kisacik B, Kul S, Zengin O. Association between red blood cell distribution width and disease activity in patients with Behçet's disease. J Int Med Res 2015; 43: 765-73.
16. Djaballah-Ider F, Touil-Boukoffa C. Effect of combined colchicine-corticosteroid treatment on neutrophil/lymphocyte ratio: a predictive marker in Behçet disease activity. Inflammopharmacol 2020; 28: 819–29.
17. Hammad M, Shehata OZ, Abdel-Latif SM, El-Din AMM. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in Behçet's disease: which and when to use? Clin Rheumatol 2018; 37: 2811-7.
18. Avci A, Avci D, Erden F, et al. Can we use the neutrophil-to-lymphocyte ratio platelet-to-lymphocyte ratio, and mean platelet volume values for the diagnosis of anterior uveitis in patients with Behcet's disease? Ther Clin Risk Manag 2017; 13: 881-6.
19. Shadmanfar S, Masoumi M, Davatchi F, et al. Correlation of clinical signs and symptoms of Behçet's disease with platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR). Immunol Res 2021; 69: 363-71.
20. Cantarini L, Pucino V, Vitale A, et al. Immunometabolic biomarkers of inflammation in Behçet's disease: relationship with epidemiological profile, disease activity, and therapeutic regimens. Clin Exp Immunol 2016; 184: 197-207.
21. Ünlü M, Arslan Z. The relation between neutrophil-lymphocyte ratio and endothelial dysfunction. Angiology 2015; 66: 694.
22. Tanacan E, Dincer D, Erdogan FG, Gurler A. A cutoff value for the Systemic Immune-Inflammation Index in determining activity of Behçet disease. Clin Exp Dermatol 2021; 46: 286-91.
23. Kim Y, Choi H, Jung SM, et al. Systemic immune-inflammation index could estimate the cross-sectional high activity and the poor outcomes in immunosuppressive drug-naïve patients with antineutrophil cytoplasmic antibody-associated vasculitis. Nephrol (Carlton) 2019; 24: 711-7.

24. Velazquez S, Madurga R, Castellano JM, et al. Hemogram-derived ratios as prognostic markers of ICU admission in COVID-19. BMC Emerg Med 2021; 21: 89.
25. Kim JW, Jung JY, Suh CH, Kim HA. Systemic immune-inflammation index combined with ferritin can serve as a reliable assessment score for adult-onset Still's disease. Clin Rheumatol 2021; 40: 661-8.
26. Ataş H, Canpolat F, Eskioglu F. Evaluation of mean platelet volume in patients with Behcet's disease as an indicator of vascular thrombosis. Arch Iran Med 2018; 21: 234-9.
27. Lippi G, Buonocore R, Cervellin G. The mean platelet volume is de- creased in patients diagnosed with venous thromboembolism in the emergency department. Semin Thromb Hemost 2016; 42: 632-5.
28. Masoumi M, Shadmanfar S, Davatchi F, et al. Correlation of clinical signs and symptoms of Behçet's disease with mean platelet volume (MPV) and red cell distribution width (RDW). Orphanet J Rare Dis 2020; 15: 297.
29. Vázquez-Santiago M, Vilalta N, Ziyatdinov A, et al. Platelet count and plateletcrit are associated with an increased risk of venous thrombosis in females. Results from the RETROVE study. Thromb Res 2017; 157: 162-4.
30. Ergelen M, Uyarel H. Plateletcrit: a novel prognostic marker for acute coronary syndrome. Int J Cardiol 2014; 177: 161.
31. Tezcan D, Özer H, Gülcemal S, et al. Diagnostic performance of lower extremity venous wall thickness and laboratory findings in the diagnosis of the Behçet disease. J Clin Rheumatol 2022; 28: e521-e527.
32. Emmi G, Becatti M, Bettiol A, Hatemi G, Prisco D, Fiorillo C. Behçet's syndrome as a model of thrombo-ınflammation: the role of neutrophils. Front Immunol 2019; 10: 1085.

Original Article

HEALTH SCIENCES
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Radiological features of round pneumonia in children: 10 years of experience

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ABSTRACT

Aim: Round pneumonia (RP) is a type of pneumonia that appears round on imaging studies and usually occurs in children. Although round pneumonia is a well-known clinical condition, few publications available in the literature describing the imaging findings and features of round pneumonia. The purpose of the review was to evaluate the chest radiographs, chest ultrasonography and CT findings associated findings of round pneumonia as compared to the published literature.

Material and Method: 65 children who were diagnosed with round pneumonia in our hospital between December 2010 and July 2020 were included in our study. Initial chest radiographs and CT scans were evaluated for lesion parameters: number, margin, opacity, size, location, and hilar LAP and air bronchogram accompaniment. Follow-up chest radiographs were evaluated for temporal variation (resolution or progression to lobar pneumonia). The findings of the patients who underwent chest ultrasonography were recorded.

Results: The mean age of the 65 children with round pneumonia included was 6.2 years and their ages ranged from 9 months to 16 years. Evaluation of chest radiographs showed one lesion in each of 63 children (96%, 63/65) and two lesions in two children (4%, 2/65). Lesion margins were sharp in 84% (55/65) and the mean diameter of lesions was 2,5 cm with a range of 1.5–9.5 cm. On the radiograph, the opacity of round pneumonia was low (60%, 39/65) and hilar lymphadenopathy was detected in 1 out of 5 patients (20%, 13/65). The location of the lesion tended to be posterior (51%, 33/65) and upper lobe (54%, 35/65). On chest ultrasonography, consalidation was seen in 8 patients, consalidation and pleural effusion were seen in 3 patients. CT images were available in 11 (17%) children. Pleural thickening or satellite lesions were not observed in any of the patients on tomography. Follow-up radiographs tended to show resolution in 95% (62/65) and progression to lobar pneumonia in 4.6% (3/65). 1 patient progressed to lobar pneumonia and died. 2 patients developed cavitary pneumonia.

Conclusion: Round pneumonia is a benign type of pneumonia that is mostly seen in children due to its physiopathology. Most patients with RP recover clinically and radiologically after antibiotic therapy. Although there are many diseases in the differential diagnosis, knowing the radiological features facilitates the diagnosis and prevents unnecessary diagnostic and imaging studies.

Keywords: Round pneumonia, children, radiology, chest radiography, computed tomography

INTRODUCTION

Round Pneumonia (RP) is a type of pneumonia that appears round on imaging studies and usually occurs in children (1). Chest radiography is the first imaging method that should be done to evaluate it diagnostically. Computed tomography (CT) is used in patients in whom the diagnosis is uncertain to exclude other diagnoses (2).

Although round pneumonia is a well-known clinical condition, few publications available in the literature describing the imaging findings and features of round pneumonia.

The purpose of the review was to evaluate the chest radiographs, chest ultrasonography (US) and CT findings associated findings of round pneumonia in 65 children as compared to the published literature.

MATERIAL AND METHOD

This retrospective study was performed in a territory children's hospital. The study was carried out with the permission of Dr. Sami Ulus Training and Research Hospital Clinical Research Ethics Committee (Date: 16.06.2021, Decision No: 2020-KAEK-141/205). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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65 children who were diagnosed with round pneumonia in our hospital between December 2010 and July 2020 were included in our study. Children with other underlying medical diseases were not included in the study.

Demographic information (age and gender) and symptoms of the patients were recorded.

The diagnosis of round pneumonia and the efficacy of treatment were evaluated by chest radiography.

Thoracic ultrasonography was performed to determine the presence and amount of fluid in cases with pleural effusion on radiographs. Thoracic CT was performed in suspected cases to exclude a non-infectious pathology and other diseases that may seen a round opacity on the chest X-ray.

Initial chest radiographs and CT scans were evaluated for lesion parameters: number, margin, opacity, size, location, and hilar LAP and air bronchogram accompaniment.

Follow-up chest radiographs were evaluated for temporal variation (resolution or progression to lobar pneumonia). The time interval between the initial and follow-up radiographs was recorded.

Chest X-ray and thoracic CT of the patients were evaluated simultaneously with consensus by a radiologist with 20 years of pediatric radiology experience and a board-certified pediatric radiologist with 3 years of experience in pediatric radiology. Thorax ultrasonography was initially interpreted in a clinical setting during patient admission by radiologist. The findings of the patients who underwent chest ultrasonography were recorded.

RESULTS

The mean age of the 65 children with round pneumonia included was 6.2 years and their ages ranged from 9 months to 16 years. Our patient population consisted of 28 females (43%) and 37 males (57%). The most common symptoms were fever (83%) and cough (64%).

Typical imaging findings are demonstrated in **Figure 1.**

Evaluation of chest radiographs showed one lesion in each of 63 children (96%, 63/65) and two lesions in two children (4%, 2/65).

Lesion margins were sharp in 84% (55/65) and ill-defined in 15% (10/65). The mean age of children with round pneumonia with a sharp margin was 4.9 years (range 10 months to 12 years) and of those with an indistinct margin 6.4 years (range 15 months to 16 years).

The mean diameter of lesions was 2,5 cm with a range of 1.5–9.5 cm. On the radiograph, the opacity of round pneumonia was low in most of the patients (39/65, %60).

Hilar lymphadenopathy was detected in 1 out of 5 patients (13/65%, 20%).

In most of the patients (37/65, 57%), no air bronchogram was seen in round pneumonia on the radiograph.

Most of the patients had two-view chest radiographs (47/65, 72%). All round pneumonic infiltrations were visible on the lateral chest radiograph. On lateral chest radiographs, the lesions were seen to be located in the anterior portion (n=13), middle portion (n=1), and posterior portion (n=33).

Specific lobar locations were left lower lobe (14), right lower lobe (11), right upper lobe (27), left upper lobe (8), right middle lobe (1), and lingula (4). In summary, the location of the lesion tended to be posterior (%,51, 33/65) and upper lobe (%54,35/65) (**Figure 2**).

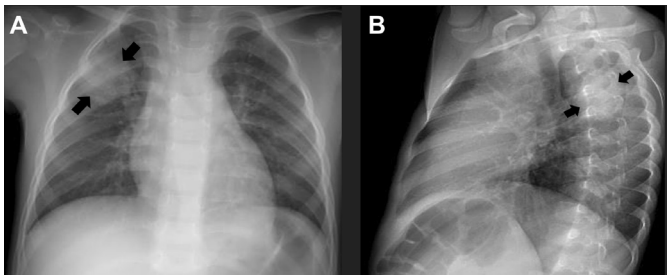

Figure 2. A 3-year-old boy with fever. Posterioranterior (A) and lateral chest radiographs (B) show well-defined, 4-cm round pneumonia in the right upper-lobe (arrows).

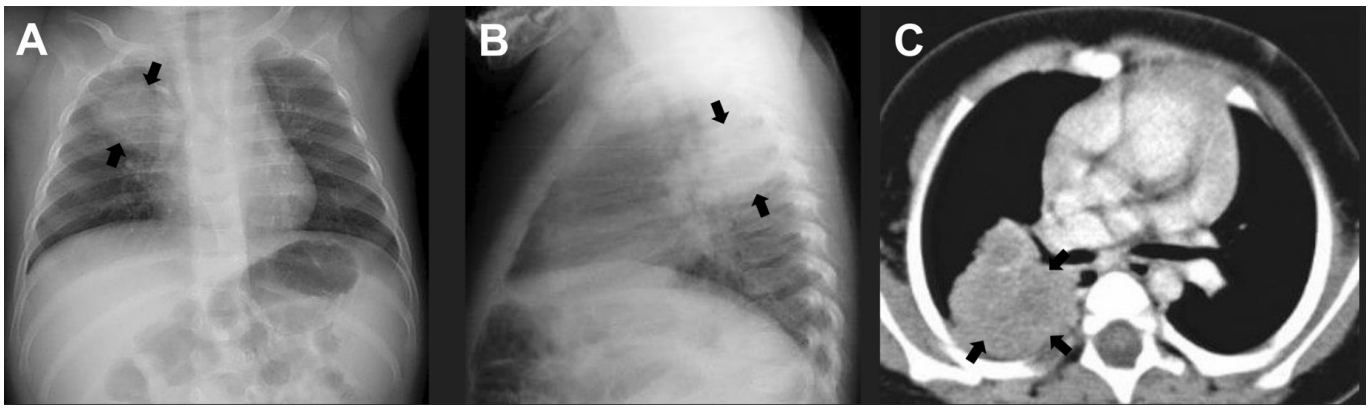

Figure 1. A 10-month-old boy with fever and cough. Posterioranterior **(A)** and lateral **(B)** chest radiographs with chest CT (mediastinal window) **(C)** show a well-defined round pneumonia (arrows) in the right upper lobe posterior segment.

Thorax ultrasonography was performed in 11 patients. Consolidation was observed in 8 of them. Consolidation with pleural effusion was seen in 3 of them.

CT images were available in 11 (17%) children. Pleural thickening or satellite lesions were not observed in any of the patients on tomography.

Follow-up chest radiographs were obtained in 49 (75%) children. Follow-up radiographs tended to show resolution in 95% (62/65) and progression to lobar pneumonia in 4.6% (3/65) (**Figure 3**). The mean time interval between initial and follow-up radiography was 15 days with a range of 4 to 45 days.

1 patient progressed to lobar pneumonia and died. 2 patients developed cavitary pneumonia.

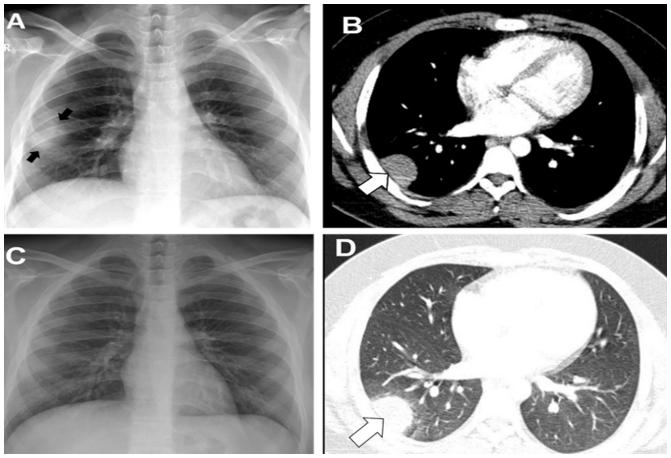

Figure 3. A round pneumonia lesion in a 16-year-old boy. İnitial posterioranterior chest radiography (A) and chest CT images (B. mediastinal window, D. lung window) show round foci of opacity (arrows) in the right upper lobe. C. Chest radiograph obtained 4 weeks later reveals resolution.

DISCUSSION

Round Pneumonia (RP) has been recognized since the 1970s as a clinical entity (1). Round pneumonia is commonly manifested in children younger than 8 years of age who have underdeveloped pathways of collateral ventilation (pores of Kohn, channels of Lambert), more closely apposed connective tissue septae and smaller alveoli compared to older children and adults (2,3). In the literature, the mean age of occurrence of round pneumonia is between 3.3 and 5 years (4,5). In our study, most of our patients (65%) were younger than 8 years old and the mean age of the patients was 6.2.

As shown in other studies, round pneumonia was seen as a solitary lesion in 96% of the cases in our study (6,7). The presence of a solitary lesion is considered a useful finding in the diagnosis of round pneumonia. Due to the poor development of collateral ventilation pathways and confinement of inflamation in adults and adolescents, more than one round lesion may be observed together (8). The ages of the children with round pneumonia, whom we saw in more than one focus in our study, were between 12 and 15 years.

Hilar lymphadenopathy may sometimes accompany round pneumonia on imaging (10). However, in the presence of hilar lymphadenopathy, causes such as tuberculosis, abscess, and fungal infections should be considered in the differential diagnosis (11). In our study, hilar lymphadenopathy was observed in 13 (20%) of our patients. While the differential diagnosis of most of these patients was made clinically, CT was performed in 3 of them.

Air bronchograms in round pneumonia on radiographs are more common in adults than in children (9,12). While the presence of air bronchogram in children suggests infection, it is absolutely necessary to make a differential diagnosis with lung cancer in adults (13). We detected air bronchogram in 37 (57%) of the patients.

In our study, the sizes of the round pneumonia lesions ranged from 1.5 to 9,5 cm and the mean diameter was 2.5 cm. These values are similar to previously reported dimensions of round pneumonia in childeren (4,14).

In our series round pneumonia lesion margins were sharp in 84% and ill-defined in 26% of the children. The mean age of children with a sharp margin (4.9 years) was less than the age of those with an indistinct margin (6.4 years). Our findings are similar to other studies (4,14). The lesion margin has been reported to be typically sharp in children.The sharp lesion margin in younger children may be associated with the underdeveloped pores of Kohn and the absence of canals of Lambert. Round pneumonia is seen less often and has ill-defined margins in children older than 8 years and in adults, who have fully developed collateral ventilation (10,14).

On radiographs, lesion opacity was found to be lower than lobar pneumonia in most of the patients (39/65, 60%). This is an important finding and fits with the pathophysiology of round pneumonia.

In studies on round pneumonia reported that the lesions tend to settle in the posterior and lower lobes. The reason for this is gravity and hypothesized that it is associated with the supine sleep position (14). However, in our study, the rates of posterior (51%) and upper lobe (54%) lesions were almost equal. This may be because the mean age of the patients in our study was higher than in other studies. As the age gets younger, sleeping on the back and the effect of gravity may increase.

Ultrasound is an easy-to-use and radiation-free imaging modality that helps evaluate the location and structure of the area of increased on chest radiography (15). We also performed chest ultrasound before CT in patients

who had round opacities with unclear borders or round opacities that we thought might be a mass on the X-ray. We performed the controls of our patients, in whom we detected consolidation and effusion, again by ultrasonography. We saw that the consolidated areas regressed sonographically before the radiography.

Chest tomography is not routinely recommended in patients with suspected RP due to unnecessary radiation exposure. We performed CT for our patients whose clinical picture was not compatible with pneumonia and whose round opacity did not improve after appropriate antibiotic treatment (16).

In previous studies, it has been reported that round pneumonia mostly improves clinically and radiographically with antibiotic therapy in both pediatric and adult patients, and rarely progresses to lobar pneumonia (4,17). In our study, a resolution of 95% (62/65) was observed in follow-up radiographs, which was consistent with the literature. Only 3 (5%) patients progressed to lobar pneumonia.

In our study, the microbiological agent causing round pneumonia was not determined, and only the radiological features of round pneumonia were described. In the literature, it has been mentioned that the etiology of round pneumonia is almost always bacterial and Streptococcus pneumoniae is the most common cause (8). On the determination of the causative microbiological agent together with the radiological features of round pneumonia studies will be helpful in determining which organism has progressed to lobar pneumonia.

Various diseases in the pediatric age group may present as intrathoracic round opacity on chest X-ray (8). Differential diagnoses of pediatric round pneumonia include fungal infection, lung abscess, tuberculosis, pulmonary malformations (sequestration, congenital cystic adenomatoid malformation and bronchogenic cyst), neoplasms (lymphoma, neuroblastoma, and chest wall tumors), and diaphragmatic hernia (8,11). Round pneumonia in children is likely to represent a benign process. Because neoplastic diseases are more common in adults and RP causes less than 1% of coin lesions in the lung (14,19). It is unlikely to be mistaken, especially with the typical clinical and radiographic appearance of round pneumonia in children. In our cases, other etiologies were not considered in the differential diagnosis because of the typical clinical and radiological findings and the regression of the findings after antibiotic treatment.

CONCLUSION

Round pneumonia is a benign type of pneumonia that is mostly seen in children due to its physiopathology. Most patients with RP recover clinically and radiologically after antibiotic therapy. Although there are many diseases in the differential diagnosis, knowing the radiological features facilitates the diagnosis and prevents unnecessary diagnostic and imaging studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dr. Sami Ulus Training and Research Hospital Clinical Research Ethics Committee (Date: 16.06.2021, Decision No: 2020-KAEK-141/205).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Kirks DR. Practical pediatric imaging: diagnostic radiology of infants and children, 1998, 3rd edn. Lippincott-Raven, Philadelphia, pp 639-42.
2. Rose RW, Ward BH. Spherical pneumonias in children simulating pulmonary and mediastinal masses. Radiology 1973; 106: 179-82.
3. Kosut JS, Kamani NR, Jantausch BA. One-month-old infant with multilobar round pneumonias. Pediatr Infect Dis J 2006; 25: 95-7.
4. Kim YW, Donnelly LF. Round pneumonia: imaging findings in a large series of children. Pediatric Radiology 2007; 37: 1235-40.
5. Fretzayas A, Moustaki M, Alexopoulou E, Liapi O, Nicolaidou P, Priftis KN. Observations in febrile children with round air space opacities. Pediatrics Int 2010; 52: 444-6.
6. Wagner AL, Szabunio M, Hazlett KS, Wagner SG. Radiologic manifestations of round pneumonia in adults. AJR.1998; 170: 723-6.
7. McLennan MK, Radiology rounds. Round pneumonia. Can Fam Physician1998; 44: 757-9.
8. Restrepo R, Palani R, Matapathi UM, Wu YY. Imaging of round pneumonia and mimics in children. Pediatr Radiol 2010; 40: 1931e40.
9. Camargos PA, Ferreira CS. On round pneumonia in children. Pediatr Pulmonol 1995; 20: 194-5.
10. Miyake H, Kaku A, Okino Y. Clinical manifestations and chest radiographic and CT findings of round pneumonia in adults. Nippon Igaku Hoshasen Gakkai Zasshi. 1999; 59: 448-51.
11. Yikilmaz, A., Lee, E. Y. CT imaging of mass-like nonvascular pulmonary lesions in children. Pediatric Radiology 2007; 37: 1253-63.
12. Hershey CO, Panaro V. Round pneumonia in adults. Arch Intern Med. 1988; 148: 1155-7.
13. Camargo JJ, Camargo SM, Machuca TN, Perin FA. Round pneumonia: a rare condition mimicking bronchogenic carcinoma. Case report and review of the literature. Sao Paulo Med J. 2008; 126: 236-8.

14. Liu YL, Wu PS, Tsai LP, Tsai WH. Pediatric round pneumonia. Pediatr Neonatol 2014; 55: 491-4.
15. Joshi P, Vasishta A, Gupta M. Ultrasound of the pediatric chest. Br J Radiol 2019; 92: 20190058.
16. Franquet T. Imaging of pneumonia: trends and algorithms. Eur Respir J 2001; 18: 196-208.
17. Silver M, Kohler S. Evolution of a round pneumonia. West J Emerg Med 2013; 14: 643-4.
18. Shady K, Siegel MJ, Glazer HS. CT of focal pulmonary masses in childhood. Radiographics 1992; 12: 505-14.
19. Arkoudis NA, Pastroma A, Velonakis G, et al. Solitary round pulmonary lesions in the pediatric population: a pictorial review. Acta Radiol Open 2019; 31: 2058460119851998.

Original Article

HEALTH SCIENCES
MEDICINE

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The factor analysis approach to mortality prediction in COVID-19 severe disease using laboratory values: a retrospective study

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ABSTRACT

Aim: Factor analysis is a statistical approach used mainly in social science scale development systems. The aim of this study was to evaluate the performance of factorial structures formed by laboratory values in predicting mortality in severe COVID-19 patients.

Material and Method: The study included 281 patients diagnosed with "severe coronavirus infection" according to the WHO COVID-19 clinical management guideline who were treated in a 13-bed adult tertiary-level critical care unit of a tertiary level hospital. For a total of 23 variables (ALT, AST, BUN, creatinine, Na, K, LDH, CRP, CK, ferritin, D-dimer, INR, TB, Glu, NLR, WBC, fibrinogen, % NEU, PLT, HTC, % LYM, TLC, Alb), laboratory values were collected. A two-step method was used to determine if exploratory factors might be used in place of laboratory variables. First, the ability of individual laboratory variables to predict mortality was obtained by analysis of the receiver operating characteristic (ROC) analysis. Then, the ability of factors created from these variables to predict mortality was measured using ROC analysis. The area under curve (AUC) values were compared between the two conditions.

Results: The Kaiser-Meyer-Olkin (KMO) value calculated using factor analysis on the variables was found to be 0.661. The significance level of the Bartlett's Test was <0.001. The correlation matrix determinant was found to be 0.001. CRP, ferritin, LDH, D-dimer, PLT, and TLC all had AUC values >0.6. A five-factor structure was created based on the Scree Plot. The fifth factor, which included CRP, fibrinogen, and ferritin, was the highest for predicting mortality (AUC: 0.677). According to the individual laboratory variables, the first factor comprising TLC, CK, and NLR, had the most remarkable success (AUC: 0,642).

Conclusions: The factor analysis approach can be used to present an alternative perspective for predicting mortality in COVID-19 critical disease. The factor including CRP, fibrinogen, and ferritin predicted mortality at the highest rate in this study.

Keywords: Coronavirus disease 2019, Covid-19, factor analysis, severe illness, mortality

INTRODUCTION

The mortality rate from coronavirus-19 (COVID-19) disease continues to increase (1). The etiology, prognostic factors, prevention, and treatment of the disease are all ongoing processes. The majority of research includes laboratory indicators, and particularly in COVID-19 disease, they are important studies performed using similar scientific procedures, in which each institution presents its own experience (2-4). Laboratory findings, such as severe lymphopenia and elevated D-dimer and ferritin levels; high C-reactive protein (CRP), lactate dehydrogenase (LDH), troponin and creatine kinase (CK) values have been related to severe COVID-19 illness (5-8).

It can be considered that the measurement methodologies of other scientific specialties might be beneficial in the COVID-19 pandemic. The factor analysis method is a multivariate data reduction method used mostly in the social sciences to identify fewer and unrelated variables (factors) by combining related variables (9). The goal of this analytic approach is to minimize the data set while keeping as much original data as reasonable.

The aim of the study was to evaluate the performance of factorial structures formed by laboratory values in predicting mortality in severe COVID-19 patients. A secondary aim of the study was to compare the performance of the factors for predicting mortality with the standard laboratory tests.

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MATERIAL AND METHOD

This single center study was ethically approved by the University of Health Sciences Turkey, Gülhane Non-interventional Clinical Researches Ethics Committee (Project No: 2021/19, Date: 14.01.2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. As this was a retrospective study, informed consent was not required.

All patients aged ≥18 years admitted to the COVID-19 tertiary-level intensive care unit, from 29th March 2020 to 06th July 2021 were included in the study. Since March 2020, this 13-bed adult tertiary-level critical care unit has been dedicated to the admission of COVID-19 patients with "severe illness" who present to the hospital.

Patients who did not have "laboratory confirmed diagnosis of SARS-CoV-2 infection"; did not stay in the intensive care unit for at least 24 hours, had missing data in the hospital records, and were transferred to other intensive care units for whatever reason; were excluded from the study.

For every patient, demographic data (age, gender), laboratory tests and patient outcomes (length of ICU stay (days), and 28-day mortality) were recorded. On a total of 23 variables, laboratory values were collected. The laboratory tests on the first day of admission to the hospital were analysed. Medical data of the patients were retrieved from the digital medical records. The laboratory tests included: alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), lactate dehydrogenase (LDH), C-reactive protein (CRP), creatine kinase (CK), ferritin, D-dimer, international normalized ratio (INR), total bilirubin (TB), glucose (Glu), neutrophil/lymphocyte ratio (NLR), white blood cells (WBC), fibrinogen, % neutrophils (NEU), platelet count (PLT), hematocrit (HTC), % lymphocyte (LYM), total lymphocyte count (TLC), and albumin (Alb).

According to the WHO guidance, "laboratory confirmed diagnosis of SARS-CoV-2 infection" was defined as a positive result of RT-PCR assay of nasal and pharyngeal swabs. "Severe illness" is characterized by clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air (10).

Statistical Analysis

Categorical variables are reported as number (%). Continuous data were reported as mean ± standard deviation (SD). Categorical data were compared using the $\chi 2$ test. The Mann-Whitney U-test was used to compare non-normally distributed continuous data. The hypothesis of a sample fit coefficient Kaiser-Meyer-Olkin (KMO) > 0.60 was used to measure the sample size fit to see if the data were acceptable for exploratory factor analysis. To evaluate whether or not there was a linear relationship between laboratory values, a correlation matrix was created. The oblimin technique, which is one of the factor rotation methods, was used in the analysis to achieve a homogenous equilibrium by ranking the independent and created factors.

To determine if exploratory factors could be employed instead of laboratory variables, the following method was performed. First, the performance of individual laboratory variables to predict mortality was determined using a receiver operating characteristic curve (ROC) analysis. Scree plot and the total variance explained table were used to determine the number of factors. The loads of laboratory variables in the factor model were measured using a rotated component matrix. Depending on the sample size, the lower power limit of the factor was determined to be 0.4. The performance of the newly developed factors to predict mortality was then determined using ROC analysis. Statistical analysis of the collected data was conducted using IBM SPSS software version 25 (SPSS Inc., Chicago, IL, USA) (11). The level of statistical significance was accepted as 0.05 in all analyses.

RESULTS

During the study period, 451 severe ill patients were admitted to the ICU, and 281 patients with laboratory confirmed diagnosis of SARS-CoV-2 infection results were analysed. 168 patients had died, corresponding to a mortality rate of 59.8%. The majority of critically ill patients with COVID-19 were males (63%). The mean age was 67.6 years. The median length of ICU stay day was 9. There was a statistically significant difference between survivors and non-survivors in terms of age and length of ICU stay (p<0.005) (**Table 1**).

Table 1. Demographic characteristics of patients (N=281)

Characteristics	Survivors N=113	Nonsurvivors N=168	P value
Female, n (%)	47 (45.2%)	57 (54.8%)	0.192*
Male, n (%)	66 (37.3%)	111 (62.7%)	0.192*
Age (years), (mean±SD)	62.26±14.25	71.2±12.03	<0.001**
ICU LOS (days), (mean±SD)	10.56±9.24	11.71±8.27	0.009**

Abbreviations: ICU:Intensive Care Unit, LOS:Length of stay, SD: Standart deviation, *Pearson Chi-Square test, **MannWhitney U test

In the factor analysis applied to the variables, the KMO value was found to be 0.661. The significance level of Bartlett's test was <0.001. These findings indicated that

there were strong correlations between some variables, indicating that the data was suitable for the factor analysis approach. The majority of the correlation coefficients between laboratory variables in the correlation matrix ranged from 0.30 to 0.80. The binary combination with the highest positive correlation coefficient in the correlation matrix was ALT and AST (correlation coefficient:0.844). Other strongly positive related binary combinations were: BUN and creatinine (coefficient: 0.746); PLT and WBC (coefficient: 0.609); % NEU and NLR (coefficıent: 0.516), CK and AST (coefficient: 0.535). The binary combinations with the highest negative correlation coefficient in the correlation matrix were: % NEU and % LENF (coefficient:-0.711) and % LYM and NLR (coefficient: -0.582). The correlation matrix determinant was found to be 0.001.

Table 2 presents the area under the curve (AUC) values and the related confidence intervals demonstrating the performance of the standard laboratory variables by the ROC analysis in predicting mortality. The variables were found to predict mortality at varying rates. The AUC values of CRP, ferritin, LDH, D-dimer, PLT and TLC were found to be > 0.6.

Table 2. Area under curve (AUC) of variables

Variables	AUC	%95 CI		P value	Sensitivity (%)	Spesificitiy (%)
		Lower limit	Upper limit			
ALT	0.466	0.396	0.536	0.352	47	34
AST	0.496	0.425	0.566	0.902	49	30
BUN	0.502	0.428	0.576	0.000	63	45
Creatinine	0.539	0.469	0.610	0.000	58	50
Na	0.500	0.429	0.572	0.256	49	39
K	0.460	0.388	0.531	0.159	26	46
CRP	0.620	0.581	0.659	0.024	63	58
CK	0.455	0.385	0.525	0.215	46	38
Ferritin	0.605	0.564	0.646	0.009	62	59
LDH	0.603	0.534	0.673	0.017	58	55
D-dimer	0.616	0.578	0.654	0.008	63	53
INR	0.579	0.509	0.649	0.031	58	56
TB	0.559	0.489	0.630	0.001	55	54
Glu	0.482	0.411	0.553	0.630	59	50
NLR	0.582	0.530	0.634	0.622	53	43
WBC	0.432	0.362	0.503	0.064	40	45
Fibrinogen	0.497	0.429	0.566	0.006	58	48
% NEU	0.463	0.393	0.533	0.430	54	52
PLT*	0.601	0.552	0.650	0.023	61	58
HTC*	0.534	0.465	0.603	0.111	30	45
% LYM*	0.558	0.488	0.628	0.152	51	39
TLC*	0.617	0.549	0.686	0.031	63	60
Alb*	0.577	0.507	0.646	0.306	54	42

* Low values are associated with mortality, ALT:alanine aminotransferase, AST:aspartate aminotransferase, BUN:blood urea nitrogen, Na:sodium, K:potassium, LDH:lactate dehydrogenase, CRP:C-reactive protein, CK:creatine kinase, INR:international normalized ratio, TB:total bilirubin, Glu:glucose, NLR:neutrophil/lymphocyte ratio, WBC:white blood cells, NEU:% neutrophils, PLT:platelet count, HTC:hematocrit, LYM:% lymphocyte, TLC:total lymphocyte count, ALB:albumin, AUC:Area under curve, CI:Confidence Interval

The number of factors that may be created using the variables when factor analysis was applied to continuous variables in the data set is shown in the Scree plot diagram in **Figure 1.** When the slope of the Scree plot generated for seventeen variables was evaluated, the slope changes up to the fifth factor, after which it forms a stable plateau. Consequently, the factors to be considered after the fifth factor will be meaningless.

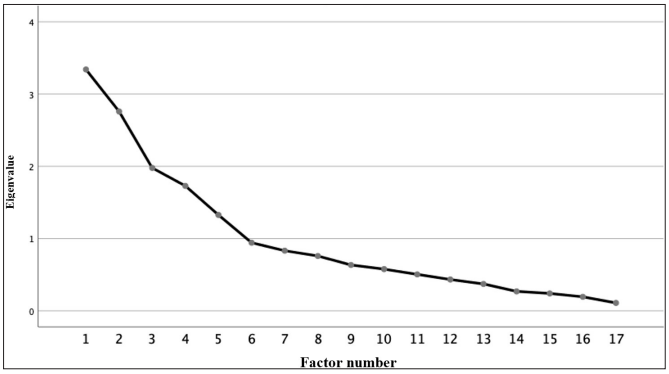

Figure 1. Scree plot diagram

Table 3 shows the number of components that may be constructed, their eigenvalues, and the total variance explained percentages. The five-factor structure accounted for 65.484% of the total variation. With a 19.648% explanatory rate among the total variance explained, the first factor is the most influencing factor structure. In the five-factor structure, there were problematic laboratory results for albumin, INR, glucose, and D-dimer, so these were removed from the analysis. **Table 4** shows the rotated componenet matrix obtained after applying the transformation, as well as the loads of variables.

Table 5 shows the ROC analysis of the factors and the variables, as well as the values of the AUC and related confidence intervals. The performance of the classification of the first and fifth factors showed the highest increase in respect of the individual performance of the variables in the ROC analysis. ROC analysis curve of fifth factor was presented in **Figure 2.** While the second factor's performance increased as the levels of AST, ALT, and % NEU increased, it performed less than the LDH value. The third factor had the lowest performance. The fourth factor's AUC was not considered successful because it was <0.6.

Table 3. Total variance explained

Factor	Total	% of Variance	% Cumulative
1	3.340	19.648	19.648
2	2.759	16.229	35.877
3	1.978	11.635	47.512
4	1.729	10.169	57.681
5	1.327	7.803	65.484

*Values obtained by rotation of oblimin technique

Tablo 4. Rotated component matrix

	Factors				
	1	2	3	4	5
TLC	-.882	-.044	.061	-.016	-.014
CK	.856	-.009	.023	.030	-.062
NLR	.747	-.088	-.041	.008	.183
AST	-.085	.934	-.053	-.082	.015
ALT	-.109	.849	-.031	-.039	-.035
% NEU	.029	.653	-.052	-.022	-.034
LDH	.115	.624	.056	.168	.111
Creatinine	.035	.086	-.873	.018	.044
BUN	.102	.106	-.863	-.007	-.073
HTC	.229	.207	.505	.177	-.263
K	.117	.041	-.440	.248	-.332
PLT	.096	-.001	.022	.798	.098
% LYM	-.397	-.021	.006	.786	-.080
WBC	.317	.000	-.046	.729	.182
CRP	.174	.036	-.086	.097	.795
Fibrinogen	.119	-.106	.076	.301	.619
Ferritin	-.091	.398	.012	-.150	.574

ALT:alanine aminotransferase, AST:aspartate aminotransferase, BUN:blood urea nitrogen, Na:sodium, K:potassium, LDH:lactate dehydrogenase, CRP:C-reactive protein, CK:creatine kinase, INR:international normalized ratio, TB:total bilirubin, Glu:glucose, NLR:neutrophil/lymphocyte ratio, WBC:white blood cells, NEU:% neutrophils, PLT:platelet count, HTC:hematocrit, LYM:% lymphocyte, TLC:total lymphocyte count, ALB:albumin, AUC:Area under curve, CI:Confidence Interval

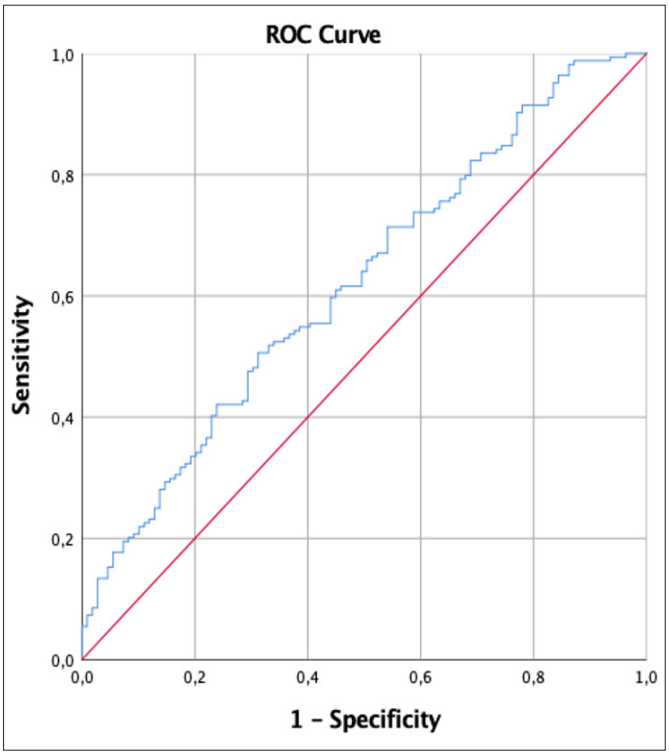

Figure 2. ROC analysis curve of 5th factor

Table 5. Area under curve (AUC) of Factors

Factors	Variables	AUC of variables (%95 CI)	AUC of factors (%95 CI)	P value (factors)	Sensitivity (%)	Spesificitiy (%)
1			0.642 (0.601-0.683)	0.032	58	56
	TLC	0.617 (0.549-0.686)				
	CK	0.455 (0.385-0.525)				
	NLR	0.582 (0.530-0.634)				
2			0.554 (0.503-0.605)	0.068	48	45
	AST	0.496 (0.425-0.566)				
	ALT	0.466 (0.396-0.536)				
	% NEU	0.463 (0.393-0.533)				
	LDH	0.603 (0.534-0.673)				
3			0.397 (0.329-0.465)	0.296	43	37
	Creatinine	0.539 (0.469-0.610)				
	BUN	0.502 (0.428-0.576)				
	HTC	0.534 (0.465-0.603)				
	K	0.460 (0.388-0.531)				
4			0.497 (0.426-0.567)	0.305	45	41
	PLT	0.601 (0.552-0.650)				
	% LYM	0.558 (0.488-0.628)				
	WBC	0.432 (0.362-0.503)				
5			0.677 (0.640-0.814)	0.007	61	59
	CRP	0.620 (0.581-0.659)				
	Fibrinogen	0.497 (0.429-0.566)				
	Ferritin	0.605 (0.564-0.646)				

ALT:alanine aminotransferase, AST:aspartate aminotransferase, BUN:blood urea nitrogen, Na:sodium, K:potassium, LDH:lactate dehydrogenase, CRP:C-reactive protein, CK:creatine kinase, INR:international normalized ratio, TB:total bilirubin, Glu:glucose, NLR:neutrophil/lymphocyte ratio, WBC:white blood cells, NEU:% neutrophils, PLT:platelet count, HTC:hematocrit, LYM:% lymphocyte, TLC:total lymphocyte count, ALB:albumin, AUC:Area under curve, CI:Confidence Interval

DISCUSSION

In this study, the performance of the factorial structure derived by laboratory values at the time of hospital admission was researched to predict the mortality of patients with COVID-19 severe disease. The factor, which included CRP, fibrinogen, and ferritin, had the highest performance level of all the factors in predicting mortality (AUC:0.677).

In the individual assessment of laboratory parameters, CRP, ferritin, D-dimer, PLT, and TLC were found to be more successful in predicting mortality than other variables, but were usually weaker indicators. The performance of these variants is in accordance with the literature on COVID-19 (12-15). However, the AUC of the variables in this and other similar studies in the literature varies. The severity of disease at the time of

hospitalization and the variety of statistical methods used are two possible explanations for these variations. In our study, severe illness was defined according to WHO COVID 19 clinical management guideline.

TLC, CK, and NLR all contributed the same factor (1st factor) structure to the five-factor structure. The AUC value of this factor was also found to be >0.6. Individually, deep and prolonged lymphopenia and high NLR have been shown to be poor prognostic indicators in severe COVID-19 disease (16,17). The factors can also be analyzed in mortality prediction models, according to their structure.

In severe COVID-19 disease, the immune response is not controlled and severe inflammation results in the release of cytokines and ARDS (18). Inflammatory cytokines such as CRP, ferritin, and IL-6 are released in greater quantities. In factor 5 in this study, CRP showed the best mortality prediction performance when combined with fibrinogen and ferritin. A consistent result is the presence of inflammatory cytokines in the same factor structure.

The concept underlying factor analysis is that there are many inter-relationships between variables (19). The data and dimensions are reduced using factor analysis by first decreasing the interdependent structures. In this regard, the relationship between the variables is investigated prior to regression analysis in the COVID-19 mortality prediction models, and if many inter-relationships are identified, a factor analysis method can also be used. In this study, a mortality prediction model was established using only laboratory variables. Many classic models, including medical history, demographics, scores, and other radiological and clinical factors, are available in the literature (20,21). The fact that other non-laboratory variables were not included in the model may be one of the reasons why the AUC values of the first and fifth factorial structures were higher than 0.6 but still low.

With the exception of scale development, only one study on COVID-19 and factor analysis was found in the literature, and that study also focused on symptom classification (22). Laboratory data were employed to predict mortality in COVID-19 severe disease in this study to determine if a different application of factor analysis might improve diagnostic classification performance.

Limitations

Limitations of this study were single center and retrospective study design, the use of only laboratory measurements, the inclusion of only patients treated in the critical care unit, and the use of laboratory variables at the time of hospital admission.

CONCLUSION

Factor analysis using laboratory and other indications may be a better predictor of mortality in severe COVID-19 disease than using these markers alone. The factor analysis method might be utilized to provide a different viewpoint on mortality prediction. The highest mortality rate was predicted by a factor structure that included CRP, fibrinogen, and ferritin. Our study is a first in this area in terms of design, because the model includes all laboratory markers, not only those found in the literature related with a poor prognosis in severe COVID-19 disease. In the next stage, an improved model incorporating categorical data linked to a poor prognosis can be established.

ETHICAL DECLARATIONS

Ethics Committee Approval: This single center study was ethically approved by the University of Health Sciences Turkey, Gülhane Noninterventional Clinical Researchs Ethics Committee (Project No: 2021/19, Date: 14.01.2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: There is no financial source of this study

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. World Health Organization (WHO). Coronavirus Disease (COVID-19) Dashboard. WHO. Accessed date: September 26 2020; Available from: https://covid19.who.int/, (n.d.).
2. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. BMJ 2020; 369: m1328
3. Doganci S, Ince ME, Ors N, et al. A new COVID-19 prediction scoring model for in-hospital mortality: experiences from Turkey, single center retrospective cohort analysis. Eur Rev Med Pharmacol Sci 2020; 24: 10247-57.
4. Sperrin M, Grant SW, Peek N. Prediction models for diagnosis and prognosis in Covid-19. BMJ 2020; 369: m1464.
5. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020; 180: 934-43.
6. Güngörer B. Baseline demographic, clinical and laboratory risk factors for predicting admission to intensive care unit in patients diagnosed with COVID-19 in the emergency department. Anatolian Curr Med J 2021; 3: 279-83.

7. Yıldırım Ö, Bayram M, Özmen RS, et al. Evaluation of hematological indices in terms of COVID-19 related mortality and ICU admission. J Health Sci Med 2021; 4: 666-9.
8. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323: 1061-9.
9. Tavşançıl E. Tutumların ölçülmesi ve SPSS ile veri analizi. Ankara, Nobel Yayın 2002
10. World Health Organization. Clinical management of COVID-19: living guidance. 25.01. 2021. WHO/2019-nCoV/clinical/2021.1
11. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.
12. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clinica Chimica Acta 2020; 506: 145-8.
13. Kırıcı Berber N, Ulutaş Ö, Sarıcı A, et al. Clinical features and laboratory values associated with disease severity in Covid 19 patients: a single center experience. J Health Sci Med 2021; 4: 18-22.
14. Antunez Muiños PJ, López Otero D, Amat-Santos IJ, et al. The COVID-19 lab score: an accurate dynamic tool to predict in-hospital outcomes in COVID-19 patients. Scientifics Reports 2021; 11: 9361.
15. Arslan K, Baş S. Frequency of troponin elevations in patients with COVID-19 and clinical course in these patients. Anatolian Curr Med J 2022; 4: 95-102.
16. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care 2020; 8: 36.
17. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med 2020; 18. 206.
18. García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. Frontiers in immunology 2020; 11: 1441.
19. Büyüköztürk Ş. Faktör analizi: temel kavramlar ve ölçek geliştirmede kullanımı. kuram ve uygulamada eğitim yönetimi. 2001; 32: 470-83.
20. Leoni MLG, Lombardelli L, Colombi D, et al. Prediction of 28-day mortality in critically ill patients with COVID-19: development and internal validation of a clinical prediction model. PLoS One 2021; 16: e0254550.
21. Altschul DJ, Unda SR, Benton J, et al. A novel severity score to predict inpatient mortality in COVID-19 patients. Scientific Reports 2020; 10: 16726.
22. Luo Y, Wu J, Lu J, et al. Investigation of COVID-19-related symptoms based on factor analysis. Ann Palliat Med 2020; 9: 1851-8.

Original Article

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Common variable immunodeficiency from the perspective of rheumatology

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ABSTRACT

Aim: Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by impaired B cell differentiation and immunoglobulin production. In addition to increased susceptibility to infection, patients with CVID have an increased tendency to autoimmune disease. Immune dysregulation in these patients may lead to granulomatous disease, malignancy, allergy and autoimmune manifestations. In this study, it was aimed to increase the awareness of rheumatologists about the main signs and symptoms of CVID.

Material and Method: Adult patients followed in the rheumatology department between January 2015 and September 2021 were included in the study. Demographic and clinical characteristics (infections, pulmonary and extrapulmonary granulomatous involvement, autoimmune manifestations), laboratory and imaging findings and treatments of the patients were analyzed.

Results: Ten adult patients with CVID were included in the study. At least one autoimmune manifestation was observed in 80% of the patients. In the follow-up period, 40% of the patients developed arthritis. Involvement of lower extremity joints such as knee and ankle was more prominent. While all patients were given 0.8 g/kg/3 weeks of intravenous immunoglobulin, 80% required immunosuppressive therapy for autoimmune manifestations.

Conclusion: Autoimmune diseases can be seen in patients with CVID, and sometimes this may be the first presentation of CVID. Heterogeneous clinical findings of the disease may lead to delay in diagnosis. Clinicians should be more careful about the different manifestations of CVID to avoid delay in diagnosis.

Keywords: Common variable immunodeficiency, arthritis, autoimmunity

INTRODUCTION

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency. Its prevalence has been reported as 1/20,000-50,000 (1). However, the prevalence is probably underestimated due to heterogeneous clinical presentations of the disease and low level of clinician awareness. CVID is characterized by low serum immunoglobulin (Ig) levels, decreased specific antibody response to polysaccharide and/or protein antigens, and increased episodes of infection in young adulthood (2). In addition to the increased susceptibility to infection, patients with CVID have a high propensity for autoimmune disease. Immune dysregulation in these patients may lead to granulomatous disease, malignancy, allergies, and autoimmune manifestations (3). Autoimmunity affects more than 30% of patients with CVID (4-6) and the likelihood of autoimmune disease in patients with CVID increases with age. Autoimmune diseases may be the first presentation of CVID (5, 7). Autoimmune disorders can be seen such as rheumatologic (systemic lupus erythematosus, rheumatoid arthritis, sicca syndrome, vasculitis), hematologic (immune thrombocytopenia, autoimmune hemolytic anemia, autoimmune neutropenia), dermatologic (alopecia, psoriasis, vitiligo), endocrinologic (hyperthyroidism, hypothyroidism), ophthalmologic (uveitis, scleritis), pulmonary (lymphocytic interstitial pneumonia) and/or gastrointestinal (inflammatory bowel disease, primary biliary cholangitis, autoimmune hepatitis, pernicious anemia, atrophic gastritis) (8). Patients are followed up in consultation with hematology, rheumatology, ophthalmology, dermatology, endocrinology and/or gastroenterology specialists for autoimmune findings.

The incidence of rheumatic disease in patients with CVID is between 5-13% (9,10). Musculoskeletal findings were observed before the diagnosis of immunodeficiency in 35% of patients with CVID who had rheumatic disease (4). In addition, rheumatological findings appear earlier than other autoimmunities. Therefore, it is critical to

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increase the awareness of rheumatologists about the main signs and symptoms of CVID and reduce the delay in diagnosis and treatment.

MATERIAL AND METHOD

The study was carried out with the permission of Dokuz Eylul University Faculty of Medicine, Non-invasive Clinical Ethics Committee (Decision No: 2022/01-28). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Adult CVID patients followed in the rheumatology-immunology outpatient clinic between January 2015 and September 2021 were included in the study. Patients were classified as CVID according to the new diagnostic criteria defined by Ameratunga et al. (11). Demographic data of the patients such as age, gender, age of symptom onset, age at diagnosis and delay in diagnosis, infections (such as sinopulmonary, gastrointestinal, genitourinary, soft tissue infections), pulmonary and extrapulmonary granulomatous involvement, autoimmune manifestations, and their treatments were investigated. Hemogram, serum Ig levels, acute phase reactants, and autoantibody profiles such as antinuclear antibody (ANA), extractable nuclear antigen antibodies (ENA), rheumatoid factor (RF), anti-cyclic citrulline peptide (anti-CCP), antineutrophil cytoplasmic antibody (ANCA) were evaluated. Low-titer autoantibody positivity due to defect in specific antibody response and hypogammaglobulinemia in patients with CVID was considered significant for the diagnosis of autoimmune disease in the presence of a appropriate clinical presentation (12).

RESULTS

Ten patients who were referred to the rheumatology outpatient clinic and followed up since 2015 were included in the study. The gender distribution of the patients was similar and the median age was 38±10.0 (min 23, max 57) years. The mean time to CVID diagnosis was 123.5±89.3 months. All patients had a history of sinopulmonary infection. A total of 40% of the patients had gastrointestinal tract infection. On the other hand, other infections (genitourinary, soft tissue, etc.) were observed in seven patients. In the examination of the chest X-ray and/or high-resolution computed tomography of the patients for pulmonary involvement, pulmonary nodules in three patients, bronchiectasis in three patients, lymphocytic interstitial pneumonia in one patient, and cavitation in one patient were detected. Half of the patients had extrapulmonary granuloma. In 80% of the patients, at least one autoimmune manifestation was observed. Autoimmune disorders such as lymphocytic interstitial lung disease, autoimmune neutropenia, thyroiditis, atrophic gastritis, scleritis, uveitis, alopecia, chronic ileitis, colitis, sicca syndrome and arthritis were seen in this study. The demographic and clinical characteristics of the patients are summarized in **Table 1**.

Table 1. Autoimmune manifestations of common variable immunodeficiency patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age/Sex	36/F	43/F	40/M	25/M	23/M	36/M	41/M	57/F	35/F	48/F
Symptom duration (years)	12	11	11	4	17	12	11	13	12	7
Diagnosis duration (years)	6	11	8	3	17	10	9	1	11	2
Sinopulmonary infection	+	+	+	+	+	+	+	+	+	+
GI infection	-	+	-	+	-	+	+	-	-	-
Other infections	+	+	-	+	+	-	+	+	-	+
Pulmonary Involvement	lymphocytic ILD	nodule	*bronchiectasis	-	-	bronchiectasis	bronchiectasis cavitation	nodule	nodule	-
Extrapulmonary Granuloma	brain parenchyma, bone marrow, liver, spleen, skin	liver, spleen	-	renal°, liver	-	**bone	-	•lymph node	-	-
Autoimmune manifestations	-	monoarthritis, chronic ileitis	oligoarthritis, atrophic gastritis, chronic ileitis	alopecia, thyroiditis, bilateral anterior uveitis	-	oligoarthritis, autoimmune neutropenia, chronic ileitis, kounis syndrome	oligoarthritis, autoimmune neutropenia	oligoarthritis, thyroiditis, sicca syndrome, recurrent scleritis	colitis	-
Cirrhosis of the liver	+	+	-	-	-	+	-	-	-	-
Lymphadenopathy	+	+	+	+	-	+	+	+	+	+
Splenomegaly	+	+	+	+	-	+	+	-	+	-
Immunosuppressive Treatment	Steroid, AZA, CSA, Adalimumab	Steroid	Steroid, SSZ	Steroid, MMF, CYC	-	Steroid, SSZ, MTX, LEF, CSA	Steroid	Steroid, MTX, AZA, CSA	Steroid, AZA	-

Abbreviations: AZA-azathioprine, CSA-cyclosporine, CYC-cyclophosphamide, F-female, GI-gastrointestinal, ILD-interstitial lung disease, LEF-leflunomide, M-male, MTX-methotrexate, SSZ-sulfasalazine, *right lower lobectomy, ** right foot 5th toe enucleation, •mediastinoscopic lymph node biopsy ° interstitial granulomatous nephritis

Allergic manifestations may also be seen in CVID and one patient had kounis syndrome (allergic angina). Three patients had chronic ileitis, while one patient had colitis. When the abdominal imaging was evaluated, cirrhotic appearance was observed in the liver in three patients. One of the patients who developed cirrhosis was decompensated with ascites. Arthritis (one monoarthritis, three oligoarthritis) was observed in 40% of the patients during the follow-up period (**Figure 1**). In patients with CVID, lower extremity joint involvement such as knee and ankle was more prevalent. Magnetic resonance imaging performed in one patient due to persistent toe pain revealed a 1x4x2 cm multiloculated cystic lesion (**Figure 2**). Granulomatoid reaction was detected in the histopathological examination. In one patient, ANA was positive with a titer of 1/100-1/320 and a speckled pattern, but his clinical presentation was not compatible with connective tissue diseases. Immunological markers such as ANA, ENA, ANCA, RF, and anti-CCP in other patients were negative. Sarcoidosis in one patient and peripheral spondyloarthritis (SpA) in another patient was considered at the first admission to the outpatient clinic; however, it was found to be CVID in the follow-up period. While all patients were given 0.8 g/kg intravenous immunoglobulin for 3-week periods, 80% required immunosuppressive therapy for autoimmune manifestations. A patient with interstitial granulomatous nephritis was undergoing 3/7 hemodialysis. One of the patients died of Pneumocystis Jiroveci pneumonia.

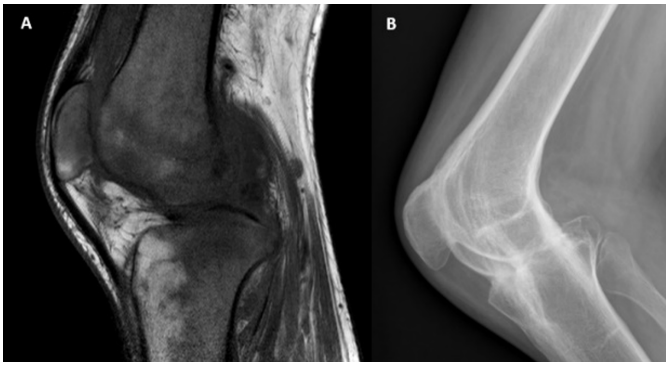

Figure 1. a. Subchondral bone marrow edema is present on the femoral and tibial surfaces adjacent to the joint. There is effusion in the joint space and lymph nodes are seen in the popliteal fossa **b.** The left tibiofemoral and patellofemoral joints are markedly narrowed.

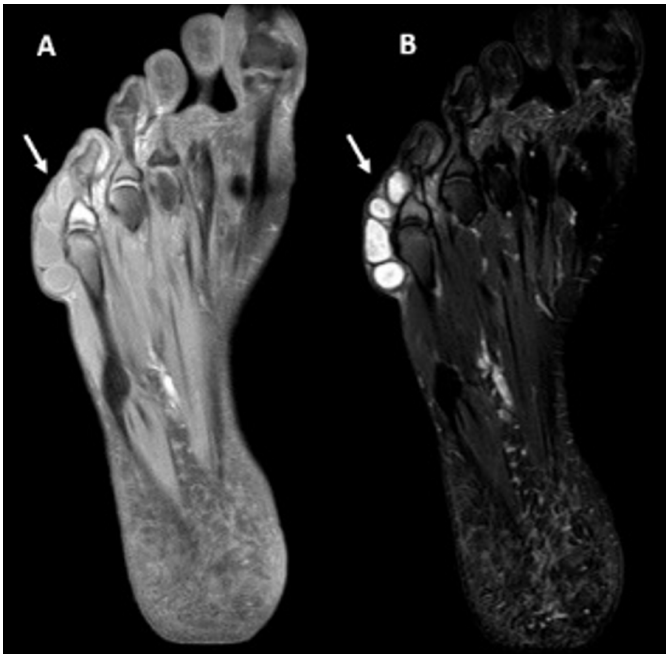

Figure 2. A sharply contoured multiloculated cystic lesion of approximately 1x4x2 cm, starting from the distal 5th tarsal bone and extending to the distal 1st proximal phalanx.

DISCUSSION

CVID is a primary immunodeficiency disease characterized by hypogammaglobulinemia, recurrent infections, and various complications. Due to the heterogeneous clinical manifestations of the disease, a delay of 6-7 years is observed in the diagnosis (13, 14). In this study, the mean time from symptom onset to the diagnosis was 27.6±24.0 months. Although the gender distribution is equal in patients with CVID, the frequency of rheumatic disease is approximately 3 times higher in women (4). In this study, however, there was no relationship between gender and the presence of arthritis.

In our study, autoimmune disorders related to different disciplines such as arthritis, alopecia, cytopenia, atrophic gastritis, ileitis, colitis, lymphocytic ILD, uveitis, scleritis, and thyroiditis were detected. The coexistence of immunodeficiency and autoimmunity seems paradoxical, leading to difficulties in the management of autoimmune complications of patients. Autoimmunity in patients with CVID has been associated with polyclonal lymphocytic infiltrative disorders, increased serum IgM levels, decreased IgE values, and decreased isotype-altered memory B cell counts (15). A wide range of rheumatological presentations can be observed in patients with CVID. Peripheral spondyloarthritis was initially considered in a male patient who presented with arthritis in the large joints of the lower extremities but was diagnosed with CVID during the follow-up period. In a study conducted in Spain, autoimmune/inflammatory manifestations were observed in one-third of 33 patients with CVID, and 6% of the patients were diagnosed with SpA (16). One of our patients was misdiagnosed as sarcoidosis because of non-caseating granuloma of the liver and lung, diffuse adenopathy, and splenomegaly. Differentiating between the granulomatous variant of CVID and sarcoidosis may also be difficult due to their overlapping clinical characteristics (17).

In the literature, it has been reported that patients with CVID are more prone to juvenile idiopathic arthritis (JIA) (18), Sjogren's syndrome (SS) (19), and systemic

lupus erythematosus (SLE) (20). In fact, coexistence of CVID and SLE is rare and the relationship between them is complex. In the case reports in the literature, the diagnosis of CVID was made after the diagnosis of SLE. When hypogammaglobulinemia occurs, some improvement may be observed in SLE presentations of some patients; however, some autoantibodies (such as ANA, anti-DNA and anticardiolipin) may be permanent despite decreased serum Ig. Moreover, it should also be kept in mind that hypogammaglobulinemia may be associated with immunosuppressive agents used in the treatment of SLE. However, hypogammaglobulinemia does not improve when immunosuppressive therapy is discontinued (21). Rheumatoid-like polyarthritis occurs in 1-10% of patients with CVID (22). In this study, polyarthritis was not observed in any of the patients, and oligoarthritis was found in 30% of the patients. In a study evaluating 248 patients with CVID, there were 2% RA, 0.8% SLE, 1.6% JIA, and 1.2% vasculitis cases (23). In the study by Resnick et al. (24) the prevalence of RA was 3.2% (n=15). It was identified that CVID patients with JRA had higher levels of transitional B cells than patients with other autoimmune complications (3). The frequency of this polyreactive transitional B cell increases 3.4 times in patients with active and treatment-naïve RA compared to the control group (25).

The risk of mortality was 11 times higher in CVID patients with non-infectious complications. Presence of chronic lung disease, lymphoma, hepatitis, gastrointestinal inflammatory disease is associated with worse survival (24). In this study, one patient died due to Pneumocystis Jiroveci pneumonia.

Inclusion of the patients referred to the rheumatology outpatient clinic only, small sample size, having a single center are limitations of the study. Further prospective multicenter studies with more patients are needed.

CONCLUSION

Autoimmune diseases can often be seen in patients with CVID, and sometimes this may be the first presentation of CVID. Rheumatological findings usually appear earlier than other autoimmunities, therefore, it is very important to increase the awareness of rheumatologists about this issue for accurate diagnosis and to prevent delay in treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dokuz Eylul University Faculty of Medicine, Noninvasive Clinical Ethics Committee (Decision No: 2022/01-28).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Valizadeh A, Yazdani R, Azizi G, Abolhassani H, Aghamohammadi A. A comparison of clinical and immunologic phenotypes in familial and sporadic forms of common variable immunodeficiency. Scand J Immunol 2017; 86: 239-47.
2. Yazdani R, Ganjalikhani-Hakemi M, Esmaeili M, et al. Impaired Akt phosphorylation in B-cells of patients with common variable immunodeficiency. Clin Immunol 2017; 175: 124-32.
3. Azizi G, Abolhassani H, Kiaee F, et al. Autoimmunity and its association with regulatory T cells and B cell subsets in patients with common variable immunodeficiency. Allergol Immunopathol (Madr) 2018; 46: 127-35.
4. Azizi G, Kiaee F, Hedayat E, et al. Rheumatologic complications in a cohort of 227 patients with common variable immunodeficiency. Scand J Immunol 2018; 87: e12663.
5. Manesh AT, Azizi G, Heydari A, et al. Epidemiology and pathophysiology of malignancy in common variable immunodeficiency? Allergol Immunopathol (Madr) 2017; 45: 602-15.
6. Azizi G, Tavakol M, Rafiemanesh H, et al. Autoimmunity in a cohort of 471 patients with primary antibody deficiencies. Exp Rev Clin Immunol 2017; 13: 1099-106.
7. Blancas-Galicia L, Ramírez-Vargas NG, Espinosa-Rosales F. Common variable immunodeficiency. A clinical aproach. Revista de Investigación Clínica 2010; 62: 577-82.
8. Gereige JD, Maglione PJ. Current understanding and recent developments in common variable immunodeficiency associated autoimmunity. Front Immunol 2019; 10: 2753.
9. Boileau J, Mouillot G, Gérard L, et al. Autoimmunity in common variable immunodeficiency: correlation with lymphocyte phenotype in the French DEFI study. J Autoimmun 2011; 36: 25-32.
10. Baldovino S, Montin D, Martino S, Sciascia S, Menegatti E, Roccatello D. Common variable immunodeficiency: crossroads between infections, inflammation and autoimmunity. Autoimmun Rev 2013; 12: 796-801.
11. Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R. New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. Clin Exp Immunol 2013; 174: 203-11.
12. Azizi G, Ziaee V, Tavakol M, et al. Approach to the management of autoimmunity in primary immunodeficiency. Scand J Immunol 2017; 85: 13-29.
13. Chapel H, Lucas M, Lee M, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood 2008; 112: 277-86.
14. Cunningham-Rundles C. How I treat common variable immune deficiency. Blood 2010; 116: 7-15.

15. Abolhassani, H., Amirkashani, D., Parvaneh, N. et al. Autoimmune phenotype in patients with common variable immunodeficiency. J Investig Allergol Clin Immunol 2013; 23: 323-9.
16. López-Aldabe K, Hidalgo L, Antolí A, Rocamora G, Corbella X, Solanich X. Op0004 Autoimmune and inflammatory manifestations in common variable immunodeficiency disorders. Ann Rheumat Dis 2021; 80: 1-2.
17. Verbsky JW, Routes JM. Sarcoidosis and common variable immunodeficiency: similarities and differences. Semin Respir Crit Care Med 2014; 35: 330-5.
18. Amer, R., Bamonte, G., Forrester, J.V. Resolution of juvenile idiopathic arthritis-associated uveitis after development of common variable immunodeficiency. SAGE Publications Sage UK: London, England 2007.
19. Lin LH, Tsai CN, Liu MF, Wang CR. Common variable immunodeficiency mimicking rheumatoid arthritis with Sjögren's syndrome. J Microbiol Immunol Infect 2005; 38: 358-60.
20. Fernández-Castro M, Mellor-Pita S, Citores MJ, et al. Common variable immunodeficiency in systemic lupus erythematosus. Semin Arthritis Rheum 2007; 36: 238-45.
21. Brandt D, Gershwin ME. Common variable immune deficiency and autoimmunity. Autoimmun Rev 2006; 5: 465-70.
22. Swierkot J, Lewandowicz-Uszynska A, Chlebicki A, et al. Rheumatoid arthritis in a patient with common variable immunodeficiency: difficulty in diagnosis and therapy. Clin Rheumatol 2006; 25: 92-4.
23. Cunningham-Rundles, C. and Bodian, C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999; 92: 34-48.
24. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012; 119: 1650-57.
25. Samuels J, Ng YS, Paget D, Meffre E. Impaired early B-cell tolerance in patients with rheumatoid arthritis. Arthritis Res Ther 2005; 7: 1-2.

Original Article

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Comparison of electrodiagnostic findings in patients with post-COVID-19 and non-COVID-19 Guillain-Barre syndrome

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ABSTRACT

Aim: The aim of this study is to compare the electrophysiological features of patients with Guillain-Barré syndrome (GBS) after Coronavirus disease–2019 (COVID-19) and the electrophysiological features of patients with non-COVID-19 GBS and to determine whether there is a difference between these two groups in terms of nerve dysfunction.

Material and Method: The electromyography results of the patients followed up with the diagnosis of GBS between December 2019 and December 2021 in the Neurology Department of Atatürk University Faculty of Medicine were retrospectively analyzed. Patients with a history of COVID-19 in the 6-week period before the occurrence of GBS were considered as the post-COVID-19 GBS group. Patients who did not have a history of COVID-19 but developed GBS were considered the non-COVID-19 GBS group. Electrodiagnostic findings of the patients were compared between two groups.

Results: Motor compound muscle action potential (CMAP) amplitude of the median nerve was detected as 1.94±1.43 mV in post-COVID-19 GBS group and 5.94±4.6 mV in non-COVID-19 GBS group ($p<0.05$). On the other hand, motor CMAP amplitude of ulnar nerve was 2.82±1.61 mV in post-COVID-19 GBS group and 6.28±4.2 mV in non-COVID-19 GBS group ($p<0.05$). Motor CMAP amplitude of the tibial nerve was detected as 1.3±1.06 mV in post-COVID-19 GBS group and 3.5±3.6 mV in non- COVID-19 GBS group ($p<0.05$). No significant difference was observed between the two groups in terms of other parameters.

Conclusion: Motor CMAP amplitudes of median, ulnar and tibial nerves were significantly low in post-COVID-19 GBS group when compared with non-COVID-19 GBS group. This result may indicate that the degree of axonal involvement and related nerve dysfunction in post-COVID-19 GBS patients in the acute period is higher than in non-COVID-19 GBS patients.

Keywords: Guillain Barre syndrome, COVID-19, EMG, CMAP, SNAP, distal latency, conduction velocity

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute immune-mediated inflammatory polyradiculoneuropathy. Progressive, symmetrical muscle weakness starting from the distal extremities and spreading to the proximal extremities, decreased, or lost deep tendon reflexes, cranial nerve palsy, bulbar symptoms, autonomic dysfunctions may be seen in GBS. The most common type of GBS is acute inflammatory demyelinating polyneuropathy (AIDP). However, there are also axonal forms such as acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN).

The diagnosis of GBS is made by the patient's clinical history and examination findings. Cerebro spinal fluid (CSF) examination and electrodiagnostic investigations are other methods which can be used to support the GBS diagnosis. Observation of no cells in CSF examination despite of increased total protein concentration in GBS is named as albuminocytological dissociation. Electrodiagnostic findings in electromyography (EMG) include, slowing of nerve conduction velocity, prolongation of distal latencies, conduction block, temporal dispersion, A-waves, prolonged or absent F wave latency and reduction of compound muscle action potential (CMAP) amplitudes in axonal forms. EMG is beneficial in determining sub-types of GBS, differential diagnosis of GBS, determining the degree of nerve dysfunction, follow-up of patients and evaluating the prognosis.

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Coronavirus disease–2019 (COVID-19); is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was first seen in December 2019 in Wuhan, caused pandemic all around the world and continues to be an important global health problem. Although COVID-19 mainly affects the respiratory system, increasing evidence shows that it may affect both the peripheral and central nervous systems (1-4).

GBS may occur between a few days to 6 weeks after Campylobacter jejuni, Cytomegalovirus, Influenza A and B, HIV and Zika virus infections. GBS cases developing after COVID-19 infection are also frequently reported (5-8). In addition to studies reporting that the clinical and prognostic features of GBS cases developing after COVID-19 are similar to non-COVID-19 GBS cases, there are also various studies showing the presence of certain differences (9,10).

The aim of this study is to compare the electrophysiological features of patients with GBS after COVID-19 and the electrophysiological features of patients with non-COVID-19 GBS and to determine whether there is a difference between these two groups in terms of nerve dysfunction.

MATERIAL AND METHOD

Ethics committee approval was obtained from the Atatürk University, Faculty of Medicine, Clinical Researches Ethics Committee (Date: 30.12.2021, Decision No: 9/17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The EMG results of the patients followed up with the diagnosis of GBS between December 2019 and December 2021 in the Neurology Department of Atatürk University Faculty of Medicine were retrospectively analyzed. The clinical and demographic characteristics of the patients, their status of having COVID-19 disease, and EMG results were recorded. Patients under the age of 18, presence of polyneuropathy, diabetes mellitus, malignancy, rheumatological disease, pregnancy, alcoholism, toxic substances, patients with metal or drug exposure that can cause polyneuropathy, those with a history of hospitalization at the intensive care unit due to COVID-19, patients with excessive extremity edema, patients with a history of previous surgery, thromboembolic event, vaccination in the last 6 weeks were excluded from the study. Files of 57 GBS patients were reviewed. Among these patients, 5 patients due to previously known polyneuropathy, 3 patients due to diabetes mellitus, 1 patient due to pregnancy, 1 patient due to rheumatoid arthritis, 2 patients due to intensive care unit stay, 2 patients due to a history of vaccination were excluded. The study was continued with 43 GBS patients who met the inclusion criteria.

GBS was diagnosed according to National Institute of Neurological Disorders and Stroke (NINDS) criteria and was confirmed by CSF examination and EMG (11). Rajabally criteria were used for the electrophysiologic diagnosis of GBS (12). Disease severity was assessed according to the Hughes functional rating scale (0=normal to 6=dead) (13).

Patients with a history of COVID-19 in the 6-week period before the occurrence of GBS were considered as the post-COVID-19 GBS group. Patients who did not have a history of COVID-19 but developed GBS were considered the non-COVID-19 GBS group. COVID-19 infection was confirmed by SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction (RT-PCR). COVID-19-PCR or COVID-19 antibody in CSF in GBS patients was not studied for economic reasons.

CSF examination was performed within 7-15 days and EMG examination was performed within 4-10 days after the onset of GBS symptoms. EMG examination was performed by the same technician by using Dantec™ Keypoint® Focus brand device after providing optimal physical conditions in neurophysiology laboratory at Atatürk University Faculty of Medicine, Department of Neurology. Low and high pass filters are set to 2 kHz-20 kHz for motor studies and 20 Hz-2000 Hz for sensory studies. The sweep speed was 2 ms/section, and the stimulus duration was 0.05-0.1 ms. Right median, ulnar and sural nerves, and right peroneal and tibial nerves were evaluated in nerve conduction studies performed in EMG. Sensory nerve conduction studies were performed antidromically in all nerves.

Sensory nerve action potential (SNAP)'s of the median and ulnar nerves were recorded from II and V fingers respectively after stimulating the nerves from the wrist. Sural SNAP was recorded at 12 cm behind the lateral malleolus after stimulating the sural nerve from the edge of Achilles tendon. The median CMAP nerve was stimulated from the wrist and elbow and recorded from the abductor pollicis brevis muscle. The ulnar CMAP nerve was stimulated above the wrist and elbow and recorded from the abductor digiti minimi muscle. Peroneal CMAP was recorded from the extensor digitorum brevis muscle by stimulating the peroneal nerve above and below the caput fibulae. Tibial CMAP was recorded from the abductor hallucis muscle by stimulating the tibial nerve from the medial malleolus and popliteal fossa. Motor and sensory distal latencies, nerve conduction velocities and CMAP amplitudes of the nerves were recorded. The results were compared between the post-COVID-19 GBS group and non-COVID-19 GBS group.

Statistical Analysis

Summary statistics of all participants were obtained based on the means and standard deviations for normally distributed data and, medians and min-max for non-normal distributed data. The distribution of normality was assessed with the D'Agostino-Pearson test. Continuous variables with normal distribution belonging to two groups were compared using the student t-test whereas non-normal distributed data were compared using the Mann Whitney U test. Two tailed p -value < 0,05 was considered statistically significant. All statistical analyzes were performed using statistical package for the social sciences for windows (SPSS 20.0).

RESULTS

There were 13 patients in the post-COVID-19 GBS group and 30 patients in the non-COVID-19 GBS group. There were 7 female and 6 male patients in the post-COVID-19 GBS group and 15 female and 15 male patients in the non-COVID-19 GBS group. The mean age of the post-COVID-19 GBS group was 58.69±17.1 years, and the mean age of the non-COVID-19 GBS group was 52.5±19.7 years (p>0.05). There was no statistically significant difference between the two groups in terms of CSF findings (p>0.05). Demographic and clinical characteristics of the patients are given in **Table 1**.

Table 1. Clinical and demographic characteristics of the patients

Characteristic	Post-COVID-19	Non-COVID-19	p
Age (mean±SD)	58.6±17.1	52.5±19.7	
Patient number (n)	13	30	
Gender (n, %)			
Female	7 (53.8)	15 (50)	
Male	6 (46.2)	15 (50)	
GBS Type (n, %)			
AIDP	7 (53.8)	17 (56.7)	
AMSAN	4 (30.8)	8 (26.7)	
AMAN	2 (15.4)	4 (13.3)	
MFS	-	1 (3.3)	
HFGSS (median, min-max)	3 (2-5)	2 (1-5)	
Treatment (n, %)			
IVIG	9 (69.2)	26 (86.6)	
Plasmapheresis	4 (30.8)	3 (13.4)	
CFS findings			
Protein (mg/dL) (median, min-max)	56.5 (42-161)	52.5 (35-198)	0.89
Glucose (mg/dL) (median, min-max)	67 (51-105)	64 (48-110)	0.25
Chloride (mmol/L) (median, min-max)	123 (119-128)	124 (117-127)	0.91

n:number, AIDP: Acute inflammatory demyelinating polyneuropathy; AMAN: Acute motor axonal neuropathy; AMSAN: Acute motor-sensory axonal neuropathy; MFS: Miller Fisher syndrome, HFGSS: Hughes functional grading scale score, IVIG: Intravenous immunoglobulin, CSF: Cerebrospinal fluid

In nerve conduction studies, motor CMAP amplitude of the median nerve was detected as 1.94±1.43 mV in post-COVID-19 GBS group and 5.94±4.6 mV in non-COVID-19 GBS group (p<0.05) (**Table 2**). On the other hand, motor CMAP amplitude of ulnar nerve was 2.82±1.61 mV in post-COVID-19 GBS group and 6.28±4.2 mV in non-COVID-19 GBS group (p<0.05) (**Table 2**).

Table 2. Motor Nerve Conduction Studies (Right)

Motor nerve conduction studies	Post-COVID-19	Non-COVID-19	p
Median CMAP Amp. (mV)	1.94±1.43	5.94±4.6	<0.001*
Median CMAP Distal Latency (ms)	5.1 (2.6-13.3)	4.22 (0-28.2)	0.64
Median NCV (m/s)	40.8 (19.8-63.9)	43.8 (0-64.1)	0.93
Ulnar CMAP Amp. (mV)	2.82±1.61	6.28±4.2	0.007*
Ulnar CMAP Distal Latency (ms)	3.9 (1.1-8.9)	3.6 (2.1-11.3)	0.8
Ulnar NCV (m/s)	47.3 (25.2-67.3)	44.9 (14.6-69.4)	0.95
Peroneal CMAP Amp. (mV)	0.8 (0-4.46)	1.4 (0-12.9)	0.13
Peroneal CMAP Distal Latency (ms)	6.3±7.1	5.5±3.1	0.6
Peroneal NCV (m/s)	32.3 (0-50)	37,4 (0-52)	0.18
Tibial CMAP Amp. (mV)	1.3±1.06	3.5±3.6	0.04*
Tibial CMAP Distal Latency (ms)	6.7±4.7	5.2±3	0.2
Tibial NCV (m/s)	37.3 (0-44.4)	36.5 (0-56.4)	0.6
Tibial F-Wave Latency (ms)	44.5 (38.2–62.5)	46.4 (32.2-65.1)	0.8

CMAP: Compound muscle action potential, NCV: Nerve conduction velocity, Amp: Amplitude, * Statistical significance

Motor CMAP amplitude of the tibial nerve was detected as 1.3±1.06 mV in post-COVID-19 GBS group and 3.5±3.6 mV in non- COVID-19 GBS group (p<0.05) (**Table 2**). Motor CMAP amplitudes of median, ulnar and tibial nerves were significantly low in post-COVID-19 GBS group when compared with non-COVID-19 GBS group. There was no statistically significant difference between the post-COVID-19 GBS and non-COVID-19 GBS groups in terms of the motor distal latencies and nerve conduction velocities of the median, ulnar, peroneal, and tibial nerves (**Table 2**). There was no statistically significant difference between the post-COVID-19 GBS and non-COVID-19 GBS groups in terms of tibial F wave latencies. In sensory nerve conduction studies, no statistically significant difference was found between the two groups in terms of SNAP amplitudes, distal latency and nerve conduction velocities of the median, ulnar and sural nerves (**Table 3**).

Table 3. Sensory Nerve Conduction Studies (Right)

Sensory Nerve Conduction Studies	Post-COVID-19	Non-COVID-19	p
Median SNAP Amp. (mV)	5,6 (0-20)	3,5 (0-23,1)	0.4
Median SNAP Distal Latency (ms)	3.04±2,2	2,15±1.96	0.2
Median NCV (m/s)	31 (0-62,5)	36,3 (0-64,5)	0.9
Ulnar SNAP Amp. (mV)	7,5±8,5	6,8±8,4	0.8
Ulnar SNAP Distal Latency (ms)	2.4±2.4	1.7±1.8	0.2
Ulnar NCV (m/s)	31 (0-62,5)	36,3 (0-64,5)	0.9
Sural SNAP Amp. (mV)	5.2±7	7.1±7.7	0.4
Sural SNAP Distal Latency (ms)	1.5±1.7	1.7±1.8	0.6
Sural NCV (m/s)	35 (0-75.7)	32.2 (0-75.8)	0.7

SNAP: Sensory nerve action potential, NCV: Nerve conduction velocity, Amp: Amplitude

DISCUSSION

In our study, the CMAP amplitudes of the median, ulnar and tibial nerves were significantly lower in post-COVID-19 GBS patients compared to the non-COVID-19 GBS group. Our study results may show that motor nerve dysfunction is significantly higher in the acute period, especially in post-COVID-19 GBS patients.

In a study comparing the electrophysiological characteristics of 24 GBS patients associated with SARS-CoV-2 with control GBS patients; there was no significant difference between the two groups in median, ulnar, peroneal, and tibial nerve CMAP amplitudes (14). In the same study; ulnar, peroneal, and tibial nerve distal motor latencies were found to be prolonged in the control GBS group when compared with the SARS-CoV-2 associated GBS group. In our study, no significant difference was found between two groups. In various studies evaluating GBS cases which has developed after COVID-19, it has been reported that the AIDP form of GBS is seen most frequently, followed by AMSAN and AMAN forms, respectively (15,16). While our study was conducted on all forms of GBS, the fact that this study was conducted only on the AIDP form of GBS and not including AMAN and AMSAN forms in the study may have caused different results for CMAP and SNAP amplitude values of nerves between two studies. Likewise, in the aforementioned study, ulnar, peroneal, and tibial nerve motor distal latencies were found to be prolonged in the control group, whereas in our study there was no difference between the two groups. This difference between studies may be related to the fact that SARS-CoV-2-associated GBS was less demyelinating and non-demyelinating forms were not included in this study.

In a case series presenting the electrophysiological features of 3 patients who developed GBS after COVID-19, CMAP amplitudes of some nerves were low, while SNAPs of many nerves could not be obtained (17). Electrophysiological data of the cases reported in this study confirmed axonal involvement in COVID-19-associated GBS and were consistent with our results.

In a study in which patients with post-COVID-19 fatigue symptoms were evaluated electrophysiologically; no difference was found for the motor conduction velocities and CMAP amplitudes of the ulnar, peroneal, and tibial nerves between groups (18). In the same study, there was no difference between the groups in terms of ulnar and sural nerve sensory conduction velocities and SNAPs. In this study, electrophysiological studies were performed 77-255 days after the onset of acute COVID-19 symptoms, and it was shown that there was no significant nerve dysfunction in COVID-19 patients without GBS. In line with these data, it can be deduced that COVID-19 does not normally cause nerve dysfunction, but a significant nerve dysfunction due to axonal neuropathy occurs in post-COVID-19 GBS patients, and the degree of this dysfunction is higher when compared with non-COVID-19 GBS patients.

CONCLUSION

Our study has limitations such as the fact that it was conducted on a small number of patients, and it did not include control EMG examinations of the patients and data on clinical prognosis. According to our research, our study is the first to show that the degree of axonal involvement and related nerve dysfunction in post-COVID-19 GBS patients in the acute period is electrophysiologically higher than in non-COVID-19 GBS patients. We believe that more comprehensive multicenter studies on this subject will be beneficial.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from the Atatürk University, Faculty of Medicine, Clinical Researches Ethics Committee (Date: 30.12.2021, Decision No: 9/17).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Portela-Sánchez S, Sánchez-Soblechero A, Melgarejo Otalora PJ, et al. Neurological complications of COVID-19 in hospitalized patients: The registry of a neurology department in the first wave of the pandemic. Eur J Neurol 2021; 28: 3339-47.
2. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Complicaciones neurológicas por coronavirus y COVID-19. Rev Neurol 2020; 70: 311-22.
3. Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA. Neurological Involvement in COVID-19 and Potential Mechanisms: A Review. Neurocrit Care 2021; 34: 1062-71.
4. Meppiel E, Peiffer-Smadja N, Maury A, et al. Neurologic manifestations associated with COVID-19: a multicentre registry. Clin Microbiol Infect 2021; 27: 458-66.
5. Caress JB, Castoro RJ, Simmons Z, et al. COVID-19-associated Guillain-Barré syndrome: The early pandemic experience. Muscle Nerve 2020; 62: 485-491.
6. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. J Neurol Neurosurg Psychiatry 2021; 92: 751-6.
7. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol 2021; 268: 1133-70.
8. 8.Kajumba MM, Kolls BJ, Koltai DC, Kaddumukasa M, Kaddumukasa M, Laskowitz DT. COVID-19-Associated Guillain-Barre Syndrome: Atypical Para-infectious Profile, Symptom Overlap, and Increased Risk of Severe Neurological Complications. SN Compr Clin Med 2020; 1-13.
9. Palaiodimou L, Stefanou MI, Katsanos AH, et al. Prevalence, clinical characteristics and outcomes of Guillain-Barré syndrome spectrum associated with COVID-19: a systematic review and meta-analysis. Eur J Neurol 2021; 28: 3517-29.
10. Gupta A, Paliwal VK, Garg RK. Is COVID-19-related Guillain-Barré syndrome different? Brain Behav Immun 2020; 87: 177-8.
11. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990; 27: 21-4.
12. Rajabally YA, Durand MC, Mitchell J, Orlikowski D, Nicolas G. Electrophysiological diagnosis of Guillain-Barré syndrome subtype: could a single study suffice? J Neurol Neurosurg Psychiatry 2015; 86: 115-9.
13. van Koningsveld R, Steyerberg EW, Hughes RA, Swan AV, van Doorn PA, Jacobs BC. A clinical prognostic scoring system for Guillain-Barré syndrome. Lancet Neurol 2007; 6: 589-94.
14. Uncini A, Foresti C, Frigeni B, et al. Electrophysiological features of acute inflammatory demyelinating polyneuropathy associated with SARS-CoV-2 infection. Neurophysiol Clin 2021; 51: 183-91.
15. Aladawi M, Elfil M, Abu-Esheh B, et al. Guillain Barre Syndrome as a complication of COVID-19: a systematic review. Can J Neurol Sci 2022; 49: 38-48.
16. De Sanctis P, Doneddu PE, Viganò L, Selmi C, Nobile-Orazio E. Guillain-Barré syndrome associated with SARS-CoV-2 infection. A systematic review. Eur J Neurol 2020; 27: 2361-70.
17. Daia C, Scheau C, Neagu G, et al. Nerve conduction study and electromyography findings in patients recovering from COVID-19 - Case report. Int J Infect Dis 2021; 103: 420-2.
18. Agergaard J, Leth S, Pedersen TH, et al. Myopathic changes in patients with long-term fatigue after COVID-19. Clin Neurophysiol 2021; 132: 1974-81.

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Evaluating the clinical, radiological, microbiological, biochemical parameters and the treatment response in COVID-19 pneumonia

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ABSTRACT

Aim: The coronavirus disease (COVID-19) has led to over 200,000,000 confirmed cases and over 4,250,000 confirmed deaths worldwide. The present study aimed to explore the links between epidemiological, clinical, biochemical, microbiological, and radiological data and treatment responses of inpatients with COVID-19 pneumonia.

Material and Method: The study included 131 patients hospitalized for COVID-19 pneumonia. Laboratory values such as complete blood count, coagulation profile, AST, LDH, sedimentation, CRP, BUN, creatinine, and D-dimer of the patients were analyzed. The diagnosis of COVID-19 was established by RT-PCR testing of respiratory tract samples. Thoracic CT images were used to determine the severity of involvement in patients. Statistical analyses were performed to establish the differences between the groups and the relationships between the variables.

Results: The most common comorbidities of the patients were hypertension (35.1%) and diabetes mellitus (24.5%). The patients with fever, cough, and dyspnea and who were PCR positive had the highest radiological involvement severity score. The involvement severity scores were negatively correlated with the lymphocyte count, lymphocyte percentage, and albumin levels ($p<0.05$). Concerning prognostic risk factors, the mean percentages of lymphocytes and eosinophils were significantly higher in the fully recovered patients than those in the intensive care unit ($p<0.05$).

Conclusion: Our study identified the percentages of lymphocytes and eosinophils as prognostic factors. Identifying the risk factors that predict the possibility of disease progression on admission may contribute to physicians' patient management, increase the therapeutic effect, and reduce the COVID-19 mortality rate.

Keywords: COVID-19, pneumonia, clinical parameters

INTRODUCTION

The coronavirus disease (COVID-19), which first appeared in China at the end of 2019, especially in Wuhan, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a betacoronavirus (1,2). COVID-19, far from being a simple upper respiratory tract infection, has become an important and urgent public health problem worldwide in the form of a pneumonia pandemic (3).

Although the first transmission was believed to be from animal to human (bat-human), the human-to-human transmission caused the disease to become a pandemic (4,5), and the high infectivity of COVID-19 caused a rapid increase in new cases and a global outbreak (6,7). It caused over 200,000,000 confirmed cases and over 4,250,000 confirmed deaths worldwide (8). Studies so far show that the disease can result in very different clinical presentations, from asymptomatic to severe pneumonia that cause multi-organ and respiratory failure (9,10). Due to asymptomatic or mild cases, the disease spreads rapidly in the community (11).

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The first confirmed case of Turkey was identified on March 10, 2020, and the first confirmed death case due to COVID-19 occurred on March 17, 2020. Currently, patient diagnosis and treatment practices in our country are carried out based on the algorithms created according to the decisions of the Ministry of Health Scientific Committee (12) and updated in line with the international literature data (13). At present, agents such as lopinavir/ritonavir, favipiravir, and remdesivir are used to treat COVID-19 pneumonia, based on observational studies and in vitro evidence in Turkey and the world (14,15). However, none of these agents directly target SARS-CoV-2, and we need more scientific evidence on how much these agents benefit patients and their confidence intervals (16).

While the exact pathophysiological mechanism of COVID-19 is still largely unknown, there are ongoing studies on a therapeutic vaccine and a specific antiviral drug at full speed, and prophylactic vaccines are currently available. Until the discovery of effective treatment, sharing clinical experiences on COVID-19 pneumonia will contribute to the efficient use of medical resources, increase the therapeutic effect, and reduce mortality.

In our study, we plan to contribute to a better understanding of the pathogenesis of the disease and treatment algorithms by sharing the epidemiological, clinical, biochemical, microbiological, and radiological data and the treatment responses of our patients treated in the hospital for COVID-19 pneumonia.

MATERIAL AND METHOD

Our study was approved by the Ministry of Health (Document No: T00_56_55) and Çanakkale Onsekiz Mart University Rectorate Clinical Researches Ethics Committee (2011-KAEK-27/2020-E.2000063714). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

Çanakkale Onsekiz Mart University Health Application and Research Hospital and Çan State Hospital were declared COVID-19 referral hospitals by our Ministry of Health on March 23, 2020.

Çanakkale Onsekiz Mart University Health Application and Research Hospital is a tertiary healthcare institution, and Çan State Hospital is a secondary healthcare institution. Both hospitals were reorganized to become an infectious disease center for the pandemic and only accepted COVID-19 patients referred by other healthcare institutions in Çanakkale province. The patients in our study were those admitted directly from the emergency department and treated in the Chest Diseases ward as inpatients with the diagnosis of COVID-19 pneumonia.

Patients and Methods

Electronic records, demographic, epidemiological, clinical, and imaging findings, treatments, complications, and outcomes of the patients treated in our ward with the diagnosis of COVID-19 pneumonia between March 27, 2020, and May 7, 2020, were collected from the Hospital Information System and analyzed retrospectively. The data collection was anonymous and patient consent was not obtained due to the retrospective nature of our study.

Inclusion criteria were being over 18 years of age and PCR positivity for COVID-19 with involvement on thoracic tomography scans compatible with COVID-19 pneumonia or PCR negativity for COVID-19 with involvement on clinical, contact information and thoracic tomography scans compatible with COVID-19 pneumonia. The exclusion criteria, in turn, were primary infection by other pathogens such as bacteria, fungi, etc.

Laboratory Findings

Laboratory values of the patients on admission were collected. The complete blood count, coagulation profile, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), sedimentation, C-reactive protein (CRP), blood urea nitrogen (BUN), creatinine, and D-dimer values were analyzed.

Oxygen saturation was measured by pulse oximetry at rest on room air and confirmed by blood gas testing. Respiratory samples including combined nasopharyngeal swabs or sputum were sent.

Respiratory samples were used to confirm the diagnosis of COVID-19 by real-time reverse transcription-polymerase chain reaction (RT-PCR). Clinical samples were analyzed in BioRad CFX-96 real-time PCR machine using Bio-Speedy SARS-COV-2 RT-qPCR detection kit with primers for the RdRp (RNA-dependent RNA polymerase) region of the virus (Bioeksen, Turkey). For the PCR assay, samples were mixed with an equal volume of vNAT solution (Bioeksen, Turkey) and analyzed using the Bio-Speedy kit as per the manufacturer's recommendations. The result was interpreted as the presence of the viral RNA if the internal control human RNase P gene was positive in the sample. The threshold value for the samples was set at 200 RFU using BioRad CFX manager software and Cq values were calculated. Samples with low Cq values were considered to have a higher viral load.

Radiological Imaging:

Thoracic computed tomography (thoracic CT) was performed on the patients in the supine position with the end-inspiration breath-holding technique by scanning from the apex to the base of the lung, without intravenous contrast.

The thoracic CT images were evaluated in five categories using the data system for COVID-19 image reporting and grading (COVID-RADS) (17). The involvement severity groups were created by dividing both lungs into three zones as upper, middle, and lower for the severity of involvement. Volumetric involvement in each zone was calculated and summed.

Statistical Method

Data were transferred to the IBM SPSS Statistics 23 program. The study data were assessed using frequency distribution for categorical variables (number, percentage) and descriptive statistics for numerical variables (mean, standard deviation).

The difference between the two groups was examined by Independent Samples t-Test and the difference between more than two groups by One-Way ANOVA. Based on the ANOVA results, a Levene's test was performed to assess the homogeneity of variances, and a multiple comparison test (Bonferroni or Tamhane's T2) was performed to identify the group(s) causing a significant difference. Differences between the groups were analyzed by the Bonferroni test for variables with homogeneous variances and by Tamhane's T2 test for variables without homogeneous variances. A Chi-square test was used to analyze the relationship between two categorical variables and a Pearson's correlation test to examine the relationship between two numerical variables.

RESULTS

The study included 131 COVID-19 pneumonia cases diagnosed clinically/radiologically and treated in the hospital. 71 (54.2%) patients had PCR positivity for COVID-19 with involvement on thoracic tomography scans compatible with COVID-19 pneumonia and 60 (45.8%) patients had PCR negativity for COVID-19 with involvement on clinical, contact information and thoracic tomography scans compatible with COVID-19 pneumonia.The demographic findings of the study patients are presented in **Table 1.**

Four patients died in the Chest Diseases clinic. These patients aged from 77 to 90 years. The comorbidities of the non-surviving patients were chronic renal failure, hypertension, chronic heart failure, Lung cancer, and gastrointestinal malignancies.

Seven of the patients transferred to the Intensive Care Unit died in the intensive care unit. The comorbidities of the patients transferred to the intensive care unit were CRF, COPD, DM, malignancies, renal transplantation, and Alzheimer's.

Table 1. Distribution of Demographics

	N	%
Sex		
Male	74	56.4
Female	57	43.6
Age	63.35±16.41	
Place of admission		
Emergency department	84	64.1
Group 1 service	45	34.3
Intensive care unit	2	1.6
CT findings on admission		
Group 2: Compatible with Bacterial Infection	2	1.5
Group 3: Compatible with Viral Pneumonia	36	27.4
Group 4: Compatible with Mixed Infection	7	5.3
Group 5: Compatible with COVID-19	86	65.6
CORADS		
2	8	6.1
3	27	20.6
4	19	14.5
5	77	58.7
Involvement severity group		
2	62	47.3
3	37	28.2
4	27	20.6
5	5	3.8
GI symptoms		
Yes	5	3.9
No	126	96.1
Respiratory rate on admission	18.99±4.27	
Systolic Blood Pressure on admission	123.86±19.88	
Diastolic Blood Pressure on admission	75.68±10.29	
Pulse on admission	95.95±17.69	
Lymphopenia		
Yes	61	46.6
No	70	53.4
History of traveling abroad in the past 14 days		
Yes	2	1.6
No	129	98.4
Intubation		
Yes	16	12.2
No	115	87.8
Length of hospital stay	6.42±3.20	
Tomography on discharge		
Same	93	71.0
Progression	1	0.8
Regression	37	28.2
Discharge		
Non-survivor	4	3.1
Full Recovery	115	87.8
Intensive care unit	12	9.2

The most common comorbidities of the patients were hypertension (35.1%) and diabetes mellitus (24.5%). These were followed by cardiovascular diseases, pulmonary diseases, and neurological diseases, respectively. The distribution of comorbidities is presented in **Table 2.**

When the patients' presenting symptoms, the severity of radiological involvement, and the PCR result were evaluated together, the patients with fever, cough, and dyspnea who were PCR positive were found to have the highest radiological involvement severity score (**Table 3**).

The one-way ANOVA for the difference in SARS-CoV-2 RT-PCR Cq values between the involvement severity groups revealed no statistically significant difference ($p>0.05$).

Similarly, Pearson's correlation analysis did not show any statistically significant correlation between radiological involvement severity scores and Cq values ($p>0.05$) (**Table 4**).

The Pearson's correlation analysis for the association of the involvement severity scores with the lymphocyte count, lymphocyte percentage, and albumin values revealed a statistically significant negative correlation ($p<0.05$) (**Table 5**). The relationship between the lymphocyte count and radiological involvement severity score in diagnosed cases was assessed by Pearson's correlation analysis. There was a statistically significant negative correlation between involvement severity scores and lymphocyte counts ($p<0.05$).

In regards to prognostic risk factors, the independent samples t-test showed a statistically significant association between the percentages of lymphocytes and eosinophils, and the type of patient discharge ($p<0.05$). Accordingly, the mean percentages of lymphocytes and eosinophils were significantly higher in patients discharged with full recovery than in those staying in the intensive care unit (**Table 6**).

Table 2. Distribution of Comorbidities

	N	%
Comorbidities		
HT	33	35.1
DM	23	24.5
Cardiovascular diseases	21	22.3
Pulmonary diseases	20	21.3
Neurological diseases	17	18.1
Psychiatric disorders	9	9.6
Malignancies	6	6.4
Hypothyroidism	4	4.3
Kidney Diseases	4	4.3
Transplantation patients	2	2.1
Gastroenterological disorders	2	2.1

b: Independent samples t-tes

Table 4. The Radiological Involvement Severity and PCR Cq association

Involvement severity group	PCR Cq Mean±SD	Test/p
2	30.93±5.67	1.047/0.367A
3	34.08±4.45	
4	34.62±3.80	
5	33.33± 3.65	
Severity score	**CQ**	
r	0.298	
p	0.110	
N	30	

A: One-way ANOVA, r: Pearson's correlation coefficient, b: Independent samples t-test

Table 6. Prognostic risk factors

	Full Recovery	Intensive care unit	Test/p
	N (%)	N (%)	
Lymphocyte count	1.26±0.67	0.95±0.58	1.540/0.127b
Lymphocytes %	18.91±10.76	12.37±6.64	2.061/0.041b
Eosinophils %	1.16±1.42	0.25±0.36	4.904/0.000b
CRP	12.43±19.88	7.82±5.13	0.798/0.426b
Ferritin	365.11±713.81	570.27±483.75	-0.741/0.461b
Fibrinogen	451.85±135.6	411.86±131.24	0.735/0.465b
D-Dimer	588.23±1041.55	1001.78±1241.63	-0.92/0.360b
Troponin	47.08±81.06	217.69±340.15	-1.498/0.172b

n: Independent samples t-test, k: Chi-square test

Table 3. Assessment of the presenting symptoms, the severity of radiological involvement, and the PCR test result

		PCR Negative				PCR Positive				Total			
		Fever	Cough	Fever + cough	Fever + cough + dyspnea	Fever	Cough	Fever + cough	Fever + cough + dyspnea	Fever	Cough	Fever + cough	Fever + cough + dyspnea
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Involvement Severity group	2	2 (40%)	7 (46.7%)	3 (75%)	1 (33.3%)	2 (25%)	7 (53.8%)	5 (55.6%)	0 (0%)	4 (30.8%)	14 (50%)	8 (61.5%)	1 (25%)
	3	2 (40%)	2 (13.3%)	0 (0%)	2 (66.7%)	4 (50%)	6 (46.2%)	0 (0%)	0 (0%)	6 (46.2%)	8 (28.6%)	0 (0%)	2 (50%)
	4	1 (20%)	6 (40%)	1 (25%)	0 (0%)	2 (25%)	0 (0%)	3 (33.3%)	1 (100%)	3 (23.1%)	6 (21.4%)	4 (30.8%)	1 (25%)
	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)
Severity score		7±4.45	7.53±5.83	6±6.68	6.67±4.51	8.75±3.41	5.54±3.1	7.33±5.85	15±4.87	8.08±3.59	6.61±4.79	6.92±5.87	8.75±5.56

Table 5. The Radiological Involvement and biochemical results association

		Severity Score			Severity Score			Severity Score
	r	-0.217		r	0.058		r	0.153
LYMPHOCYTE count	p	0.023	ALT	p	0.515	LDH	p	0.086
	N	110		N	129		N	128
	r	-0.211		r	0.099		r	-0.049
LYMPHOCYTES %	p	0.017	AST	p	0.268	CRP	p	0.588
	N	127		N	128		N	126
	r	0.009		r	-0.059		r	0.104
Respiratory rate	p	0.921	Urea	p	0.508	Procalcitonin	p	0.396
	N	129		N	129		N	69
	r	0.023		r	0.034		r	0.101
Total Leukocyte count	p	0.794	Creatinine	p	0.703	Sedimentation	p	0.371
	N	127		N	129		N	81
	r	0.076		r	-0.261		r	-0.149
Neutrophil count	p	0.428	Albumin	p	0.003	Troponin	p	0.221
	N	112		N	128		N	69
	r	0.098		r	0.179		r	0.102
Neutrophils %	p	0.271	Bilirubin	p	0.070	CK-MB	p	0.479
	N	129		N	103		N	50
	r	0.005		r	0.027		r	-0.042
Eosinophil count	p	0.956	Na	p	0.762	Ferritin	p	0.716
	N	108		N	129		N	78
	r	0.041		r	-0.145		r	0.054
Eosinophils %	p	0.670	K	p	0.104	D-DIMER	p	0.639
	N	108		N	128		N	77
	r	-0.046		r	-0.122		r	-0.130
PLATELETS	p	0.604	Cl	p	0.641	Fibrinogen	p	0.308
	N	129		N	17		N	63

r: Pearson's correlation coefficient

DISCUSSION

The patients we followed up in the Chest Diseases ward of Çanakkale Onsekiz Mart University Medical Faculty Hospital and Çan State Hospital were referred to us from the surrounding districts and villages due to COVID-19 pneumonia and respiratory failure. Therefore, our study patients were older than the China-based cohorts, with a mean age of 63.35 + 16.41 years, and had more comorbidities (100%) (18-20). However, the mean age of our patients was similar to that of the patients in the COVID-19 studies conducted in the European and American populations (21,22). In our study, male patients accounted for 56.4% of the study sample. This rate was similar to those reported by the studies from China (58%), Italy (60%), and New York (56%) (19,23,24).

In our study, the leading comorbidities of the patients followed up with COVID-19 pneumonia were hypertension (HT) (35.1%) and diabetes mellitus (DM) (24.5%), which were followed by cardiovascular diseases, pulmonary diseases, and neurological diseases, respectively. Our results were in line with the results of a meta-analysis involving a systematic literature review that concluded a high prevalence of hypertension and diabetes among comorbidities in patients with COVID-19 (25). The results of another systematic literature review and meta-analysis study, in agreement with our study, also showed that the most common comorbidity among patients with confirmed COVID-19 infection was HT, followed by cardiovascular diseases and diabetes, and concluded that it was associated with significant morbidity in patients with chronic diseases (26). A meta-analysis study by Sanyaolu et al. (27) found that 88.8% and 68% of COVID-19 patients had fever and cough, respectively. In our study, 73% of the patients had a fever and 67% had a cough. The same study examined comorbidities associated with COVID-19, observing that COVID-19 had a more severe course in older adult patients, and identifying the comorbidities associated with COVID-19 as hypertension (15.8%), cardiovascular diseases (11.7%), and diabetes mellitus (9.4%) . Another study examined the biopsy results of 26 patients who died after SARS-CoV-2 infection. Accordingly, 65.4% of the patients had arterial hypertension, 38.5% had obesity, 34.6% had chronic ischemic heart disease, and 15.4% had Type 2 diabetes. The autopsy results showed that 92.3% of the patients had coronary artery disease (28). The study by Cummings et al. (29) with data on 1150 hospitalized COVID-19 patients reported that older age, chronic

heart disease, and high concentrations of D-Dimer were associated with mortality. These studies and our study show that comorbidities such as hypertension, cardiovascular diseases, and DM are particularly common in COVID-19 patients and negatively affect the course of the disease.

Studies have demonstrated that the disease progresses more severely and mortality is higher in COVID-19 patients with diabetes. It has been shown that COVID-19 patients with diabetes but without any other comorbidity are at greater risk of severe disease when assessed by organ injury, inflammatory factors, and hypercoagulation (30). In two different clinical trials conducted in the USA with COVID-19 patients admitted to the ICU, the rate of diabetes mellitus was found to be 58% and 33%. This may be related to glucotoxicity resulting from impaired glucose metabolism in patients with diabetes mellitus, and endothelial injury resulting from overreacting inflammatory responses (31,32). In our study, diabetes mellitus was detected in 24.5% of the COVID-19 patients and was a common comorbidity.

The four patients who died in our clinic had a higher mean age than other patients and had CRF, HT, CHF, lung cancer, and GI malignancies as comorbidities. The comorbidities identified in the patients with a deteriorating condition while receiving treatment in our clinic and thus were transferred to the intensive care unit were CRF, COPD, DM, malignancies, renal transplantation, and Alzheimer's disease. Seven of the patients transferred to the intensive care unit died in the intensive care unit. The rate of transfer to the intensive care unit was 9.2%, and the overall mortality, including the patients transferred to the intensive care unit, was 8.4% in our study. A study conducted to examine mortality rates in the USA in 2020 with 20736 patients compared the mortality rates on admission from March 2020 to November 2020 and determined that the mortality rate was 19.1% between March and April 2020 while decreasing to 10.8% between September and November 2020 (33).

A retrospective study of 1057 patients showed that PCR Ct values, which indicate the viral load, were not associated with patients' need for oxygenation (34). This finding is similar to our finding indicating no correlation between PCR Ct values and radiological findings. However, our study, when evaluating the patients' presenting symptoms, the severity of radiological involvement, and the PCR result together, found that the patients with fever, cough, and dyspnea who were PCR positive had the highest radiological involvement severity score. This suggests that a higher rate of positive PCR tests may be detected in symptomatic patients.

In our study, we observed that the count and percentage of lymphocytes on hospital admission were negatively correlated with radiological involvement in COVID-19 patients. We also identified the lymphocyte percentage as a prognostic factor in COVID-19 patients, and we observed that patients with a high lymphocyte percentage had a lower risk of admission to the ICU. In the early months of the outbreak, Guan et al. (19) described the clinical characteristics of 1,099 patients with laboratory-confirmed COVID-19 from 552 hospitals in China until January 29, 2020. Lymphopenia was detected in 82.1% of patients, and leukocyte/lymphocyte counts in the blood and the chest X-ray/CT findings were found to be associated with poor clinical outcomes. Similarly, Wagner et al. (35) reported that a low lymphocyte count and lymphopenia were more common in COVID-19 patients admitted to the ICU than in non-admitted patients. The same study also observed more common acute kidney injury in COVID-19 patients with lymphopenia. Another study with 306 patients found a low lymphocyte count (< 790/mm^3) to be associated with mortality and the need for mechanical ventilation (36). Various mechanisms have been proposed for the occurrence of lymphopenia in COVID-19 patients. It is believed that cytokines such as TNF-alpha and IL-6 produced in the cytokine storm seen in COVID-19 patients cause the death of considerable lymphocytes by apoptosis in lymphoid organs. In addition, an increase has been observed in receptors such as PD-1, which leads to the depletion of T lymphocytes, in the cell membranes of T lymphocytes in COVID-19 patients (37). Lymphopenia and low T lymphocyte counts have almost always been observed in severe COVID-19. When these findings are evaluated together, lymphocyte percentage on hospital admission appears to be an important prognostic factor.

Our study also identified the percentage of eosinophils as a prognostic factor in COVID-19 patients, as is the case with the percentage of lymphocytes, and observed that patients with a high percentage of eosinophils had a lower risk of admission to the intensive care unit. Similarly, a study of 97 COVID-19 patients found that patients with low eosinophil counts on hospital admission had more severe symptoms, more lesions in the lung, and longer hospital stays (38). Another study with 190 patients, in turn, observed that the eosinophil count was lower in the critically ill COVID-19 patients than those with mild and severe COVID-19, and showed that a decrease in eosinophil count was associated with mortality (39).

A study of 189 patients investigating albumin levels in COVID-19 patients found that patients with high albumin levels on hospital admission had a lower risk of acute respiratory distress syndrome and ICU admission (40). A study involving 299 patients showed

an association between a low albumin level and mortality in COVID-19 patients. It is believed that the low albumin levels of these patients may result from severe systemic inflammation (41). According to our data, there was a negative correlation between the albumin level and the severity of radiological involvement.

Our study has some limitations. First, the sample size was small, including patients only from two centers in Çan Province. Studies that include more patients and centers may be needed. Adding other specific markers to our study may further increase sensitivity and specificity. Antiviral agents and corticosteroid use were not included as variables in this study. It would not be healthy to generalize without supporting the data obtained in this study with more comprehensive studies; however, the results of our study seem to be consistent with the current literature.

CONCLUSION

Increasing numbers of cases and clinical experience have led to more detailed information about COVID-19 pneumonia. Our study identified the percentages of lymphocytes and eosinophils as prognostic factors. It would be useful to clarify independent high-risk factors and accurately estimate the progression of COVID-19 by multivariate analysis. Therefore, identifying risk factors that predict the possibility of disease progression on admission would help physicians to decide which patient groups can be safely managed in district hospitals and who should be transferred early to tertiary care centers. This may allow the efficient use of medical resources, improve the therapeutic effect, and reduce the COVID-19 mortality rate. The predictions of prognostic factors in this study would help guide ongoing response efforts, as well as provide accurate and efficient healthcare resources needed in times of sudden rises of cases

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Ministry of Health (Document No: T00_56_55) and Çanakkale Onsekiz Mart University Rectorate Clinical Researches Ethics Committee (2011-KAEK-27/2020-E.2000063714).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Sun P, Lu X, Xu C, et al. Understanding of COVID-19 based on current evidence. J Med Virol 2020; 92: 548-51.
2. Zhu N, Zhang D, Wang W, et al. A Novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.
3. Health Mo. Ulusal Pandemi Hazırlık Planı Secondary Ulusal Pandemi Hazırlık Planı 2019. https: //hsgm.saglik.gov.tr/tr/bulasicihastaliklar-haberler/ulusal-pandemi-hazirlik-plani.html
4. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet (London, England) 2020; 395: 514-23.
5. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-73.
6. Lillie PJ, Samson A, Li A, et al. Novel coronavirus disease (COVID-19): The first two patients in the UK with person to person transmission. J Infect 2020; 80: 578-606.
7. Spina S, Marrazzo F, Migliari M, et al. The response of Milan's Emergency Medical System to the COVID-19 outbreak in Italy. Lancet (London, England) 2020; 395: e49-e50.
8. WHO. Coronavirus disease (COVID-19) pandemic. Secondary coronavirus disease (COVID-19) pandemic 2021. https: //www.who.int/emergencies/diseases/novel-coronavirus-2019.
9. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J=Xianggang yi xue za zhi 2003; 9: 399-406.
10. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenzaa. Clin Infect Dis 2019; 68: e1-e47.
11. Hoehl S, Rabenau H, Berger A, et al. Evidence of SARS-CoV-2 Infection in returning travelers from Wuhan, China. N Engl J Med 2020; 382: 1278-80.
12. Bakanlığı TCS. COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi (Bilim Kurulu Çalışması). Secondary COVID-19 (SARS-CoV-2 Enfeksiyonu) Rehberi (Bilim Kurulu Çalışması) 2020. https: //covid19bilgi.saglik.gov.tr/depo/rehberler/COVID-19_Rehberi.pdf.
13. Lazzerini M, Putoto G. COVID-19 in Italy: momentous decisions and many uncertainties. Lancet Global Health 2020; 8: e641-e42.
14. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discovery 2020; 6: 16.
15. Schrezenmeier E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nature Rev Rheumatol 2020; 16: 155-66.
16. McCreary EK, Pogue JM. Coronavirus Disease 2019 treatment: a review of early and emerging options. Open Forum Infect Dis 2020; 7: ofaa105.
17. Salehi S, Abedi A, Balakrishnan S, et al. Coronavirus disease 2019 (COVID-19) imaging reporting and data system (COVID-RADS) and common lexicon: a proposal based on the imaging data of 37 studies. Eur Radiol 2020; 30: 4930-42.
18. Cao J, Tu WJ, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 2020; 71: 748-55.

19. Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-20.
20. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020; 395: 497-506.
21. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of COVID-19 in New York City. N Engl J Med 2020; 382: 2372-74.
22. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020; 323: 1574-81.
23. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. Jama 2020; 323: 1335.
24. Rosenberg ES, Dufort EM, Blog DS, et al. COVID-19 testing, epidemic features, hospital outcomes, and household prevalence, New York State-march 2020. Clin Infect Dis 2020; 71: 1953-59.
25. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020; 94: 91-95.
26. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020; 34: 101623.
27. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med 2020: 1-8.
28. Elezkurtaj S, Greuel S, Ihlow J, et al. Causes of death and comorbidities in hospitalized patients with COVID-19. Scientific Reports 2021; 11: 4263.
29. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet (London, England) 2020; 395: 1763-70.
30. Lim S, Bae JH, Kwon H-S, et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 2021; 17: 11-30.
31. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020; 323: 1612-14.
32. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020; 382: 2012-22.
33. Roth GA, Emmons-Bell S, Alger HM, et al. Trends in patient characteristics and COVID-19 in-hospital mortality in the United States during the COVID-19 pandemic. JAMA Network Open 2021; 4: e218828-e28.
34. Abdulrahman A, Mallah SI, Alqahtani M. COVID-19 viral load not associated with disease severity: findings from a retrospective cohort study. BMC Infect Dis 2021; 21: 688.
35. Wagner J, DuPont A, Larson S, et al. Absolute lymphocyte count is a prognostic marker in COVID-19: a retrospective cohort review. Int J Lab Hematol 2020; 42: 761-65.
36. Andrés M, Leon-Ramirez J-M, Moreno-Perez O, et al. Fatality and risk features for prognosis in COVID-19 according to the care approach – a retrospective cohort study. PLOS ONE 2021; 16: e0248869.
37. Tavakolpour S, Rakhshandehroo T, Wei EX, et al. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. Immunol Lett 2020; 225: 31-32.
38. Xie G, Ding F, Han L, et al. The role of peripheral blood eosinophil counts in COVID-19 patients. Allergy 2021; 76: 471-82.
39. Yan B, Yang J, Xie Y, et al. Relationship between blood eosinophil levels and COVID-19 mortality. World Allergy Organization J 2021; 14: 100521.
40. Kheir M, Saleem F, Wang C, et al. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. Plos One 2021; 16: e0248358.
41. Huang J, Cheng A, Kumar R, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. J Med Virol 2020; 92: 2152-58.

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Morphological and immunohistochemical evaluation of interface lesions between chronic lymphocytic thyroiditis and papillary thyroid cancers

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ABSTRACT

Objective: To evaluate the expression of papillary thyroid carcinoma-associated tumor markers in reactive and dysplastic changes showing papillary thyroid carcinoma-like nuclear features in chronic lymphocytic thyroiditis cases.

Material and Method: In this study, we retrospectively analyzed 84 cases diagnosed with chronic lymphocytic thyroiditis based on the analysis of thyroidectomy specimens in our center over the last five years. We classified them as normal, reactive and dysplastic changes and performed an immunohistochemical analysis using HBME-1, Galectin-3, Cytokeratin 19, and Cyclin D1.

Results: The mean age of the patients was 45.5 years, and 68 were female and 16 were male. According to the morphological features, 42.9% of the were classified to have normal morphology, 44.0% reactive atypia, and 13.1% follicular epithelial dysplasia (FED). Of the chronic lymphocytic thyroiditis cases, 42.9% were associated with malignancy, with the most common accompanying malignancy being papillary thyroid cancer (36.9%). Immunohistochemically: for HBME-1, FED (72.7%) was higher ($p<0.05$) than normal and reactive atypia (0.0%); for Galectin-3, FED (63.6%) was higher ($p<0.05$) than normal and reactive atypia (0.0%); for Cytokeratin 19, Reactive atypia (75.7%) and FED (90.9%) were higher than normal (44.4%); and for Cyclin-D1, Reactive atypia (62.2%) and FED (81.8%) were higher than normal (33.3%).

Conclusions: We consider that reactive and dysplastic changes including papillary thyroid carcinoma-like nuclear changes may support preneoplastic changes in terms of morphology and immunoprofile in chronic lymphocytic thyroiditis cases.

Keywords: Thyroid cancer, follicular epithelial dysplasia, chronic lymphocytic thyroiditis

INTRODUCTION

Thyroid cancer is the most common type of endocrine cancer with the highest incidence and prevalence worldwide (1). The precursor lesions of thyroid neoplasms may originate from C cells or follicular cells. The role of C-cell hyperplasia as a precursor lesion of medullary thyroid carcinoma has been extensively explored. Despite the common of follicular epithelial cell-derived neoplasms, the precursor lesions of follicular epithelial cell origin were not elucidated until the Chernobyl nuclear power plant accident, and dysplastic or preneoplastic follicular lesions were not well defined (2).

The detection of precursor lesions is the most effective approach to improve the treatment of tumors and reduce their morbidity. The recognition of precursor lesions in the uterine cervix allows for the development of successful screening programs. Similarly, while progress has been made in other organs, including the breast, colon, and urinary tract, an important limitation remains in identifying precursor lesions in the thyroid. Dysplasia as an interface between normal histology and carcinoma in the thyroid gland is still a controversial issue (3).

Due to several epidemiological similarities between chronic lymphocytic thyroiditis and papillary thyroid carcinoma (PTC), it has been suggested that chronic lymphocytic thyroiditis is an endogenous carcinogen for thyroid cancer (4). In chronic lymphocytic thyroiditis, follicular epithelial cells may show histomorphologically nuclear features resembling PTC. The term follicular epithelial dysplasia (FED) was first used by Chui et

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al. (5), who defined it as a putative precursor lesion of papillary carcinoma in chronic lymphocytic thyroiditis. FED lesions are defined as atypical cell foci that differ from the surrounding parenchyma, are smaller than 1 mm, and have moderate cytological atypia and architectural distortion. Atypical cells consist of irregular membranes, mild to moderate nuclear enlargement and clearing, a groove, and crowded nuclei with chromatin margination. These lesions are distinguished from papillary microcarcinoma by their infiltrative growth pattern, absence of stromal desmoplasia and intranuclear pseudoinclusions, and the presence of surrounding intense lymphocytic inflammation (5).

In PTC, HBME-1, Cytokeratin 19, and Galectin-3 have been proven to be the most promising immune markers due to their high sensitivity and specificity (6,7). Cyclin D1, which is involved in the regulation of the cell cycle, has been reported to be overexpressed in PTC (8).

In this study, we evaluated the morphological and immunohistochemical features of FED with markers used in PTC in chronic lymphocytic thyroiditis samples diagnosed in our center over the last five years.

MATERIAL AND METHOD

The study was carried out with the permission of the Turkish Ministry of Health Ankara Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.10.2021, Decision No: 769-2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 120 patients who underwent total thyroidectomy/lobectomy in our center and were diagnosed with chronic lymphocytic thyroiditis over the last five years were retrospectively analyzed. Thirty-six cases whose specimens could not be reached, whose immunostained sections were lost, or who had tissue shedding due to technical reasons were excluded from the study. In the remaining 84 cases, thyroid follicle epithelial cells in the inflammation areas consisting of lymphocytes in the thyroid parenchyma were evaluated morphologically.

The diagnosis of chronic lymphocytic thyroiditis was based on the presence of lymphoplasmacytic infiltration between thyroid follicles with or without a germinal center. Inflammation was evaluated as mild if the inflammation is focally in groups among the follicular, and intense if it is widespread in the parenchyma with prominent germinal centers.

The parenchyma was divided into 3 groups using the criteria described by Chui et al. and evaluating the structurally/cytological appearance; normal parenchyma, reactive atypia and FED (5).

Normal parenchyma (**Figure 1A**): Structurally and cytological preserved normal-appearing thyroid follicle epithelial cells adjacent to lymphocytic inflammation.

Reactive atypia (**Figure 1B**): Structurally; Follicles that do not contain papillary structures and vary slightly in size and shape. Cytological; Round slightly enlarged nuclei slight nuclear membrane. irregularity, rare grooves, nuclear clearing, and cells showing slight crowding/overlapping.

FED (**Figure 1C**): Structurally; Irregularly shaped follicles, trabecular, solid sockets without papillary structure. Cytological; Cells containing grooves, often showing nuclear clearing, nuclear membrane irregularity, and overlapping, slightly to moderately enlarged, lost nuclear roundness.

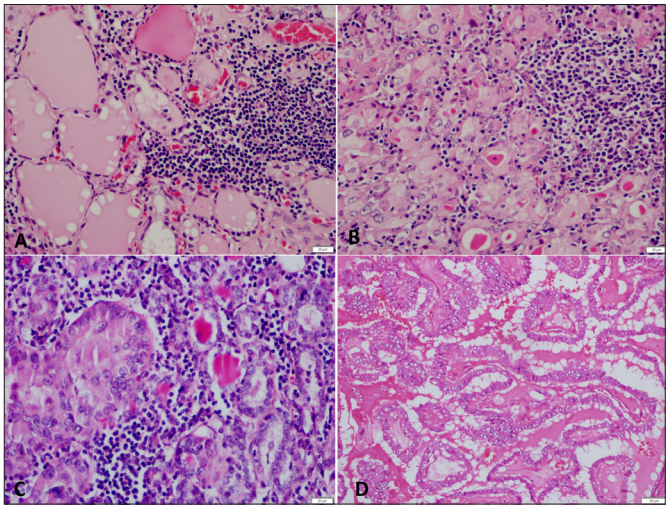

Figure 1. Morphological spectrum of atypical follicular epithelial lesions in chronic lymphocytic thyroiditis. (A) normal morphology (H&E, x40), (B) reactive atypia (H&E, x40), (C) follicular epithelial dysplasia (H&E, x40), (D) papillary thyroid carcinoma (H&E, x200).

Formalin-fixed, paraffin-embedded tissue sections of 4 micron were prepared using the Leica HRP conjugated compact polymer system detection dab kit (Leica DS9800, New Castle, UK) on the Leica bond max automated IHC/ISH system. HBME-1 (clone HBME1, Dako), Galectin-3 (clone 9c4, Leica), Cytokeratin 19 (clone b170, Leica), and Cyclin-D1 (clone EP12, Leica) were immunohistochemically applied.

The evaluation of immunostaining was performed by an independent pathologist blinded to the clinical and pathological data. The presence of cytoplasmic staining with Galectin-3, cytoplasmic/membranous staining with Cytokeratin 19, apical staining with HBME-1, and nuclear staining with Cyclin-D1 was evaluated. Staining intensity: 0; negative, 1; weak, 2; medium, 3; strong; as a percentage of staining, more than 10% was considered positive 5. Normal thyroid tissue was focally positive for Cyclin D1 and Cytokeratin 19, and negative for HBME-1 and Galectin-3.

Statistical Analysis

Data were analyzed using SPSS software package (version 22.0; SPSS, Inc., Chicago, IL, USA) and expressed as number, percentage and mean±standard deviation values as applicable. The Pearson chi-square analysis was performed to evaluate the relations between the groups. In cases where the expected value is less than 5 in more than 20% of the sections, the Fisher Exact Test was applied instead of Pearson Chi-Square. A p value of less than 0.05 was considered statistically significant.

RESULTS

The age of the patients with chronic lymphocytic thyroiditis ranged from 17 to 73 years, and the mean age was 45.4±13.16 years. 81 % (n=68) of the cases were female and 19% (16) were male. Seventy-six (90.5%) samples were total thyroidectomy and the remaining cases were lobectomy.

In chronic lymphocytic thyroiditis samples, relatively normal follicles were found in areas of mild inflammation, while atypia findings were observed in follicle epithelial cells adjacent to lymphoid aggregates. According to morphological features, 42.9% (n=36) of the patients were classified to have normal morphology, 44.0% (n=37) reactive atypia, and 13.1% (n=11) FED (**Figure 1**). No statistically significant difference was observed between the lesions and accompanying malignancy. (p=0.346). Two or more foci were detected in 32.2% of the cases with reactive atypia and 6.8% of those with FED. The size of the reactive atypia foci was 0.1mm-3.6 mm, and that of the FED foci was 0.1 mm-2.4 mm. The FED size did not significantly differ between the groups (p=0.367), and there was no statistical relationship between multifocality and concomitant neoplastic pathology (p=0.051).

The lesions observed adjacent to chronic lymphocytic thyroiditis and the accompanying benign and malignant lesions were compared. In cases of chronic lymphocytic thyroiditis, malignancy association was found at a rate of 42.85%, and the most common accompanying malignancy was PTC at a rate of 36.9%. A PTC association was present in 40.5% of the samples containing reactive atypia and 36.4% of those containing FED. PTC in reactive atypia; NIFTP and FTC in FED accompanied Chronic lymphocytic thyroiditis more than other groups (p<0.05) (**Table 1**). In a total of 31 cases, PTC was associated with chronic lymphocytic thyroiditis. The staining profiles of these cases with HBME-1, Galectin-3, Cytokeratin 19 and Cyclin D1 are summarized in **Table 2** and presented as an image in **Figure 2.**

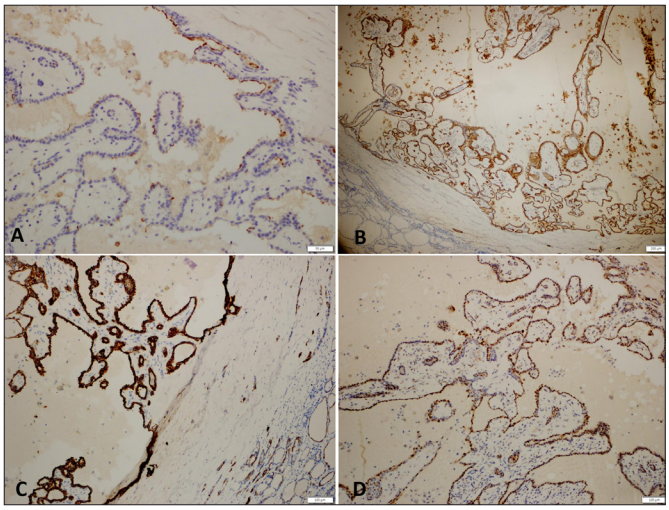

Figure 2. Papillary thyroid carcinoma. (A) HBME-1, x200 (B) Galectin-3, x40 (C) Cytokeratin 19, x100 (D) Cyclin D1, x100.

Table 1. Benign and malignant lesions accompanying chronic lymphocytic thyroiditis

Chronic lymphocytic thyroiditis (n=84)	Coexistence of benign and malignant lesions	Total, n (%)
Normal morphology, n=36		
	Benign lesions (FA/HCA/NH)	24 (66.7%)[a]
	NIFTP	0 (0%)[a]
	PTC	12 (33.3%)[a]
	FTC	0 (0%)[a]
Reactive atypia, n=37		
	Benign lesions (FA/HCA/NH)	19 (51.4%)[a]
	NIFTP	1 (2.7%)[a]
	PTC	15 (40.5%)[b]
	FTC	2 (5.4%)[a]
FED, n=11		
	Benign lesions (FA/HCA/NH)	4 (36.4%)[a]
	NIFTP	2 (18.2%)[b]
	PTC	4 (36.4%)[a]
	FTC	1 (9.1%)[b]

Each subscript letter denotes a subset of "Coexistence of benign and malignant lesions" categories whose column proportions do not differ significantly from each other at the ,05 level. FED: Follicular epithelial dysplasia. FA: Follicular adenoma. HCA: Hurthle cell adenoma. NH: Nodular hyperplasia NIFTP: non-invasive follicular thyroid neoplasm with papillary-like nuclear features. PTC: Papillary thyroid carcinoma. FTC: Follicular thyroid carcinoma.

Table 2. Results of the immunohistochemical analysis of papillary thyroid carcinomas

Immunostaining	Positive (n, % of evaluated cases)
HBME-1	25/31 (80.6%)
Galectin-3	24/31 (77.4%)
Cytokeratin 19	29/31 (93.5%)
Cyclin-D1	27/31 (87.1%)

We also analyzed Cytokeratin 19, galectin-3, HBME-1 and Cyclin D1 that are markers known to be associated with PTC and lesions observed in chronic lymphocytic thyroiditis. The Immunohistochemical profiles of chronic lymphocytic thyroiditis lesions are summarized in **Table 3**. A statistically significant difference was observed in HBME-1, Galectin-3, Cytokeratin 19 and Cyclin D1 according to the presence of FED (**Figure 3**). While there was medium (+2) staining with Galectin-3 in FED lesions, more intense (+3) staining was detected with HBME-1, Cytokeratin 19, and Cyclin D1. Mild staining with Cyclin D1 was observed in 62.2% of the reactive atypia lesions and moderate staining with Cytokeratin 19 in 75.7%. No staining with HBME-1 and Galectin-3 was detected in reactive atypia lesions (**Figure 4**). Mild staining with Cytokeratin 19 and Cyclin D1 was detected in thyroid follicle epithelial cells with normal morphology at a rate of 44.4% and 33.3%, respectively. No staining was observed with HBME-1 and Galectin-3.

In brief, FED foci observed in chronic lymphocytic thyroiditis tissues shared similar morphologies and immune phenotypes with PTC.

Table 3. Results of the immunohistochemical analysis of chronic lymphocytic thyroiditis

Lesion	HBME-1	Galectin-3	Cytokeratin 19	Cyclin-D1
Normal morphology, n=36	0/36 (0%)[a] 0	0/36 (0%)[a] 0	16/36 (44.4%)[a] +1 (15/16) +2 (1/16)	12/36 (33.3%)[a] +1 (12/12)
Reactive atypia, n=37	0/37 (0%)[a] 0	0/37 (0%)[a] 0	28/37 (75.7%)[b] +1 (4/37) +2 (24/37)	23/37 (62.2%)[b] +1 (19/23) +3 (4/23)
FED, n=11	8/11 (72,7%)[b] +2 (2/8) +3 (6/8)	7/11 (63.6%)[b] +1 (2/7) +2 (5/7)	10/11 (90.9%) [b] +2 (2/10) +3 (8/10)	9/11 (81.8%)[b] +2 (1/9) +3 (8/9)
p value	0.001	0.001	0.003	0.005

Each subscript letter denotes a subset of "Lesions" categories whose column proportions do not differ significantly from each other at the ,05 level. FED: Follicular epithelial dysplasia.

DISCUSSION

In 1863, German pathologist Rudolf Virchow suggested the presence of lymphocytes in neoplastic tissues and indicated a relationship between cancer and inflammation (9). Chronic inflammation is considered to contribute to approximately 25% of all malignancies (10). Although many epidemiological studies have reported that the risk of PTC is increased with chronic lymphocytic thyroiditis, the relationship between chronic lymphocytic thyroiditis and PTC is still debated due to many conflicting results (11,12). The epidemiological association of chronic lymphocytic thyroiditis and PTC has been reported with a frequency of up to 38% with no evidence (12,13). Consistent with the literature, in our study, up to 43% of the chronic lymphocytic thyroiditis cases were associated with malignancy, with the most common accompanying malignancy being determined as PTC at a rate of 36.9%. It has been suggested that due to the relative prevalence of both diseases, this may be an accidental association or chronic inflammation may lead to the development of neoplastic transformation (4,14). In addition, it is still controversial whether there is an immunological link between the two diseases based on their simultaneous developments. Uncertainties remain in the development of papillary carcinoma concerning the immune escape mechanism, target-specific immune response, or cross-reacting antitumor immunity (15). Recent gene expression experiments have also demonstrated a strong correlation between the expression of immune lymphocytic infiltrates in the thyroid and error-prone DNA repair (16). In the study of Kholova et al., the size of FED lesions ranged from 0.1 to 3.5 mm, and it was frequently found to be multifocal in 45.1% of the samples (17). In our study, the size of FED foci were in the range of 0.1-2.4mm, and 2 or more

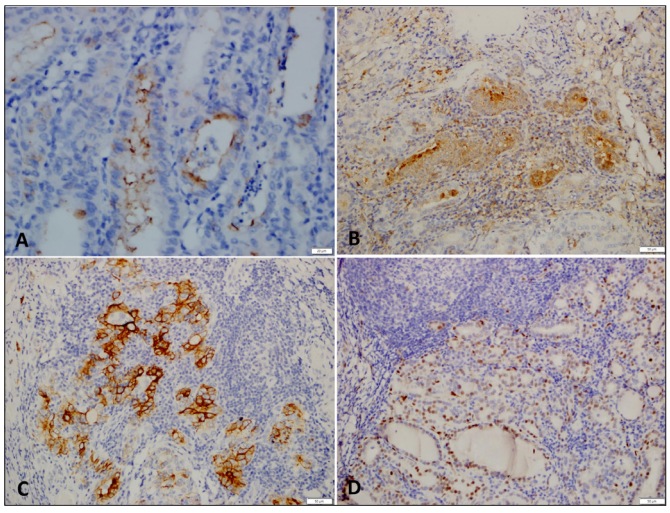

Figure 3. Follicular epithelial dysplasia. (A) HBME-1, x400 (B) Galectin-3, x200 (C) Cytokeratin 19, x200 (D) Cyclin D1, x200.

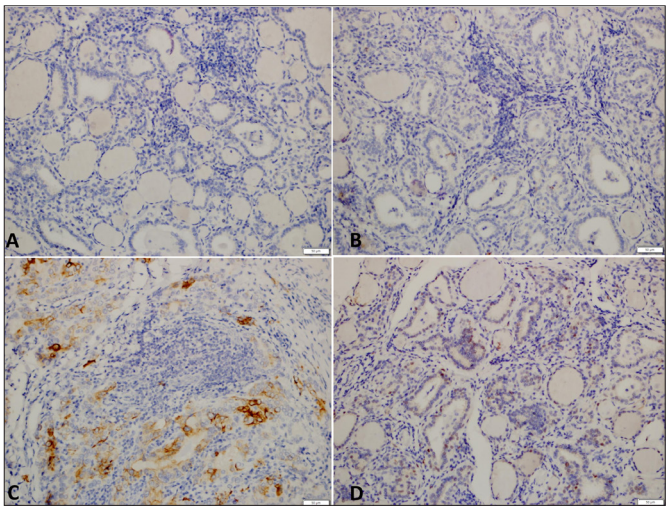

Figure 4. Reactive atypia. (A) HBME-1, x200 (B) Galectin-3, x200 (C) Cytokeratin 19, x200 (D) Cyclin D1, x200.

foci were detected in 6.8%. Although it was similar in size to the literature, a lower rate was observed in terms of multifocality. It may be due to the small number of FED lesions in the study group.

In chronic lymphocytic thyroiditis, atypia of the follicular epithelium, which has similar appearance to PTC nuclear features, is common, especially in areas of intense inflammation (18). Some authors have suggested that these atypical cells may represent the precursor lesion of PTC (5,19). Dysplasia and/or precursor lesions in the background of thyroiditis have been described as FED (5). FED lesions and PTC immunoprofile have also been found to be similar in various studies. Chui et al. (5) showed that these atypical proliferations exhibited an immunohistochemical profile similar to PTC with strong staining with HBME-1, galectin-3, CK19 and Cyclin D1 and supported the presence of a premalignant lesion. In another study, Ma et al. (20) revealed the increased expression of PTC-related markers, such as CK19, galectin-3, HBME-1, CD56, claudin 1, and NGAL in atypical follicular epithelial foci in Hashimoto's thyroiditis cases compared to peritumoral benign thyroid tissues. In a similar study, Prasad et al. (21) reported an increased expression of Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 in follicle epithelial cells with papillary-like nuclei in chronic lymphocytic thyroiditis (21). Kholová et al. (17) found a high expression of Cyclin D1, Galectin-3, Cytokeratin 19 and HBME-1 in FED foci and noted the presence of a significant relationship between Cyclin D1 and FED accompanied by PTC.

In our study, there was more frequent staining with Cytokeratin 19 and Cyclin D1 in patients with reactive atypia and FED. In FED lesions, staining with HBME-1 and Galectin-3 was similar to the PTC cases. The staining pattern of the FED lesions was similar to PTC. Our findings support the idea that follicular epithelial cells with normal morphology and reactive atypia and FED lesions may represent a neoplastic spectrum during PTC development and, as previously suggested (5), FED may be a precancerous lesion in terms of morphology and immune profile.

Molecular and immunohistochemical studies to detect specific gene profiles and related proteins in thyroid cancer have been extensively reported in the literature. Nasr et al. (22) suggested that atypical cells found in Hashimoto's thyroiditis showed HBME1 and CK19 expressions but could not be considered preneoplastic because they did not harbor BRAF mutations.

The earliest molecular event in PTC is RET/ PTC gene rearrangement, which is a common finding in encapsulated papillary thyroid carcinoma, papillary thyroid microcarcinoma, and Hashimoto's thyroiditis. RET/PTC gene rearrangement is highly specific for PTC and associated with the characteristic nuclear features seen in this disease (23). However, low-level RET-PTC recombination has also been demonstrated in hyperplastic thyroid nodules (24,25). A study in the PTC series showed that RET/PTC rearrangement was more common in autoimmunity-associated PTC, whereas the BRAFV600E mutation was more common only in PTC. There was an overlap in the molecular profile of PTC and Hashimoto's thyroiditis, as well as similarities in morphological features and immunohistochemical staining patterns (26–28). One of the main limitations of the study is that the tissues are exposed to fixation and follow-up methods in different time periods due to their retrospective nature. Therefore, due to the small size of the lesions during the immunohistochemical examination, problems such as shedding of the tissue and disappearance in the section were experienced due to technical reasons. This has resulted in fewer cases. Another limitation is the lack of molecular data on patients. Papillary thyroid carcinoma is diagnosed definitively by detecting the BRAFV600E mutation combination, which is known to be associated with malignancy, together with morphological examination. It is also important to look for the BRAFV600E mutation for possible precursor lesions of PTC.

We consider that normal-reactive-dysplastic changes observed in patients with chronic lymphocytic thyroiditis may also support molecular changes in the PTC spectrum in terms of their morphology and immune profile.

CONCLUSION

The relationship between chronic lymphocytic thyroiditis and papillary thyroid carcinoma, and the concept of 'follicular epithelial dysplasia' as a possible precursor lesion are very controversial among researchers. Chronic inflammation can be a risk factor for the development of PTC. Due to the similarity of the morphological and immunohistochemical features of FED to PTC, the former can be considered as an interface or a precancerous lesion between chronic lymphocytic thyroiditis and PTC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Turkish Ministry of Health Ankara Training and Research Hospital Clinical Researches Ethics Committee (Date: 20.10.2021, Decision No: 769-2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, 2021. Access date: 12.10.2021.
2. Canberk S. Precursor and borderline lesions of the thyroid (indolent lesions of epithelial origin): from theory to practice. Gland Surg 2020; 9: 1724-34.
3. Kumar V, Abbas AK, Aster JC. Robbins & Cotran Pathologic Basis of Disease. 9th Edition. Ellsevier Health sciences 2020.
4. Jankovic B, Le KT, Hershman JM. Clinical review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? J Clin Endocrinol Metab 2013; 98: 474–82.
5. Chui MH, Cassol CA, Asa SL, Mete O. Follicular epithelial dysplasia of the thyroid: morphological and immunohistochemical characterization of a putative preneoplastic lesion to papillary thyroid carcinoma in chronic lymphocytic thyroiditis. Virchows Arch 2013; 462: 557–63.
6. Paunovic I, Isic T, Havelka M, Tatic S, Cvejic D, Savin S. Combined immunohistochemistry for thyroid peroxidase, galectin-3, CK19 and HBME-1 in differential diagnosis of thyroid tumors. Apmis 2012; 120: 368–79.
7. de Matos PS, Ferreira AP, de Oliveira FF, Assumpcao LV, Metze K, Ward LS. Usefulness of HBME-1, cytokeratin 19 and galectin-3 immunostaining in the diagnosis of thyroid malignancy. Histopathology 2005; 47: 391–401.
8. Temmim L, Ebraheem AK, Baker H, Sinowatz F. Cyclin D1 protein expression in human thyroid gland and thyroid cancer. Anat Histol Embryol 2006; 35: 125-9.
9. Virchow R. Die Krankhaften Geschwulste. Aetologie der neoplastichen Geschwulste/Pathogenie der neoplastischen Geschwulste. Verlag von August Hirschwald, Berlin 1863.
10. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. Int J Cancer 2007; 121: 2373–80.
11. Noureldine SI, Tufano RP. Association of Hashimoto's thyroiditis and thyroid cancer. Curr Opin Oncol 2015; 27: 21-5.
12. Pusztaszeri MP, Faquin WC, Sadow PM. Tumor-associated inflammatory cells in thyroid carcinomas. Surg Pathol Clin 2014; 7: 501-14.
13. Guarino V, Castellone MD, Avilla E, Melillo RM. Thyroid cancer and inflammation. Mol Cell Endocrinol 2010; 321: 94-102.
14. Boi F, Pani F, Mariotti S. Thyroid autoimmunity and thyroid cancer: review focused on cytological studies. Eur Thyroid J 2017; 6: 178-86.
15. Ehlers M, Schott M. Hashimoto's thyroiditis and papillary thyroid cancer: are they immunologically linked? Trends Endocrinol Metab 2014; 25: 656-64.
16. Nicolson NG, Brown TC, Korah R, Carling T. Immune cell infiltrate-associated dysregulation of DNA repair machinery may predispose to papillary thyroid carcinogenesis. Surgery 2020; 167: 66–72.
17. Kholová I, Kalfert D, Lintusaari J, Rajakorpi E, Ludviková M. Follicular epithelial dysplasia as hashimoto thyroiditis-related atypia: a series of 91 specimens. Endocrine Pathology 2021; 32: 368–74.
18. Berho M, Suster S. Clear nuclear changes in Hashimoto's thyroiditis. A clinicopathologic study of 12 cases. Ann Clin Lab Sci 1995; 25: 513-21.
19. Di Pasquale M, Rothstein JL, Palazzo JP. Pathologic features of Hashimoto's-associated papillary thyroid carcinomas. Hum Pathol 2001; 32: 24-30.
20. Ma H, Yan J, Zhang C, et al. Expression of papillary thyroid carcinoma-associated molecular markers and their significance in follicular epithelial dysplasia with papillary thyroid carcinoma-like nuclear alterations in Hashimoto's thyroiditis. Int J Clin Exp Pathol 2014; 7: 7999-8007.
21. Prasad ML, Huang Y, Pellegata NS, de la Chapelle A, Kloos RT. Hashimoto's thyroiditis with papillary thyroid carcinoma (PTC)-like nuclear alterations express molecular markers of PTC. Histopathology 2004; 45: 39-46.
22. Nasr MR, Mukhopadhyay S, Zhang S, Katzenstein AL. Absence of the BRAF mutation in HBME1+ and CK19+ atypical cell clusters in Hashimoto thyroiditis: supportive evidence against preneoplastic change. Am J Clin Pathol 2009; 132: 906–12.
23. Arif S, Blanes A, Diaz-Cano SJ. Hashimoto's thyroiditis shares features with early papillary thyroid carcinoma. Histopathology 2002; 41: 357–62.
24. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014; 159: 676–90.
25. Jung CK, Little MP, Lubin JH, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of BRAF mutations and a sharp increase in RAS mutations. J Clin Endocrinol Metab 2014; 99: E276-85.
26. Muzza M, Degl'Innocenti D, Colombo C, et al. The tight relationship between papillary thyroid cancer, autoimmunity and inflammation: clinical and molecular studies. Clin Endocrinol (Oxf) 2010; 72: 702-8.
27. Kang DY, Kim KH, Kim JM, et al. High prevalence of RET, RAS, and ERK expression in Hashimoto's thyroiditis and in papillary thyroid carcinoma in the Korean population. Thyroid 2007; 17: 1031-8.
28. Sargent R, LiVolsi V, Murphy J, Mantha G, Hunt JL. BRAF mutation is unusual in chronic lymphocytic thyroiditis-associated papillary thyroid carcinomas and absent in non-neoplastic nuclear atypia of thyroiditis. Endocr Pathol 2006; 17: 235–41.

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Comparison of the in vitro *Demodex folliculorum* killing activity of azelaic acid and permethrin

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ABSTRACT

Aim: *Demodex* parasites have been linked to dermatological disorders, especially rosacea, without a proven mechanism. Moreover, some anti-*Demodex* agents demonstrate a dual therapeutic effect related to a direct effect on the skin disorder along with a decreased number of *Demodex* mites. Despite being considered a first-line treatment approach for rosacea, azelaic acid's efficacy against *Demodex* mites has not been investigated. In the current study, mites were continuously observed after exposure to the test agents to evaluate the potential anti-*Demodex* efficacy of azelaic acid. The efficacy of azelaic acid was compared to that of a positive control agent (permethrin).

Material and Method: The wastes of diagnostic standardized skin surface biopsy samples of rosacea patients were collected for the trial. To four active treatment groups were administered 10% azelaic acid, 20% azelaic acid, 30% azelaic acid, and 5% permethrin. In addition, there was a control group, and 20 *Demodex* mites were included in each of the five groups. The authors conducted the real-time observation of the study groups through a digital microscope. The survival times of the mites were recorded and compared between the groups.

Results: The mean survival time was 12.2±1.5 minutes in the 5% permethrin group. The mean survival times in the 10%, 20%, and 30% azelaic acid groups were 15.8±1.6, 14±1.5, and 12±1.2 minutes, respectively. The differences between the four active treatment groups did not reach statistical significance ($p>0.05$).

Discussion: The present study's results revealed that all three concentrations of azelaic acid had anti-*Demodex* efficacy comparable to that of 5% permethrin.

Keywords: *Demodex*, rosacea, topical treatment

INTRODUCTION

Demodex mites reside in hair follicles and sebaceous glands and survive by the ingestion of keratin and sebaceous secretions. The presence of *Demodex* mites in healthy humans is common. However, they are linked to severe infestations that result in mortality in animals (1). Thus, in contrast to the established pathogenic potential in animals, they are mostly accepted as commensals in humans (2). Among the mites that settle on the skin, such as Sarcoptes scabiei hominis, *Cimex lectularius*, and *Dermatophagoides pteronyssinus*/*farinae*, *Demodex* mites are less immunogenic and harmless, rarely causing immunological or allergic reactions (3).

In humans, *Demodex* mites localized at the mother's nipple pass from mother to infant shortly after birth (4). *Demodex* mites contain lipase enzymes and they tend to settle in seborrheic areas, especially the facial skin. Activation of the sebaceous glands in adolescence creates a relatively favorable microenvironment for the development of *Demodex* mites, and an increase in *Demodex* density is observed during this period. While the incidence is 13% in the population between 3 and 15 years old, it reaches 95% in those over 70 (4, 5).

Demodex mites have been linked to various ophthalmological and dermatological disorders (4, 6-8). Although a causal explanation has yet to be established, several studies have demonstrated that *Demodex* density was substantially increased in rosacea, perioral dermatitis, and folliculitis patients compared to age- and sex-matched control groups (8-11). *Demodex* mites were hypothesized to cause permanent microabrasions within the skin of rosacea patients. Accordingly, the deterioration of the skin barrier might contribute to cutaneous hypersensitivity. Hence, a reduction in *Demodex* density might relieve the symptoms and provide better disease control in rosacea patients.

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Although it is possible to detect *Demodex* mites through histopathological examination of punch biopsy samples, the ideal diagnostic method for cutaneous demodicosis is the standardized superficial skin biopsy (SSSB) (12). The skin surface biopsy, which was first described in 1971, was revised by Forton and Says in 1993 and later renamed the SSSB (14, 15). For this practical, noninvasive technique, a 1 cm2 square is drawn on a slide. After cyanoacrylate is dripped onto this site, the slide is attached to the target sample collection area and kept in the same region for 60 seconds. After that, the slide is gently removed and the sample is examined by direct microscopy. This method can detect large numbers of *Demodex* mites and the movement of these mites can be easily observed due to their relatively large size. Although a dermatologist can easily perform the technique even in a first-line hospital setting, studies on acaricidal agents' in vitro anti-*Demodex* effect are very limited. In the study by Kligman et al., in which double-sequence standardized skin surface biopsy techniques were described, the average survival time of *Demodex* mites obtained by this method was 3 hours in olive oil. In comparison, it was less than 2 hours in mineral oil (10). This suggests that a follow-up period of approximately three hours would be sufficient to evaluate the efficacy of any treatment agent on *Demodex*.

A limited number of studies on aromatic oils' in vitro anti-*Demodex* activity have been published (16-22). In these studies, eyelash samples were exposed to the treatment agents. However, it was stated that parasites embedded in highly keratinized hair samples would be protected against drug penetration. Recently, our research group conducted an in vitro experiment on the wastes of SSSB samples of rosacea patients (23). We compared the anti-*Demodex* efficacy of tea tree oil to that of permethrin (positive control) and immersion oil (negative control). By using this approach, we detected a dose-related response pattern for tea tree oil. The survival time of the negative control group was 196 minutes, which was compatible with the available data (23).

The data for *Demodex* treatment approaches are quite limited. An in vitro study conducted in 1981 revealed that metronidazole, which is considered in the forefront of anti-*Demodex* treatments, did not alter the survival of *Demodex* mites even at high doses such as 1 mg/kg (24). Thus, the efficacy of metronidazole has been associated with an independent anti-inflammatory action rather than a direct acaricidal effect (24). Recently, it has been suggested that the successful treatment results obtained with ivermectin in rosacea cases may be related to the combination of a decrease in *Demodex* density and an anti-inflammatory effect (25). The intertwining of different mechanisms makes it difficult to determine whether the positive result obtained is due to the acaricidal effect or the direct effect of the drug on the underlying dermatological disease.

Conversely, accepted treatment alternatives for rosacea may also have direct anti-*Demodex* efficacy. Azelaic acid (1,7-heptanedicarboxylic acid) is a naturally occurring saturated dicarboxylic acid (26, 27). The anti-inflammatory, antibacterial, and antikeratinizing effects of azelaic acid have been described. It can inhibit tyrosinase, which is involved in the production of melanin, and also 5α-reductase, which is related to androgenetic alopecia (26, 27). It has been used in various formulations to treat rosacea, acne, and melasma. Azelaic acid 15% gel has been approved by the US Food and Drug Administration for the topical treatment of inflammatory papules and pustules of mild to moderate rosacea (28). There have been no reports on the anti-*Demodex* efficacy of this agent. The aim in the present study was to investigate azelaic acid's in vitro *Demodex* killing activity by using our recently published technique.

MATERIAL AND METHOD

The University of Health Sciences Gülhane Scientific Researches Ethics Committee approved the study (Date: 06.01.2022, Decision No: 2022/10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Materials

The study agents, topical permethrin 5% solution and azelaic acid, were provided by the company Jeomed (Istanbul, Turkey). Azelaic acid in 10%, 20%, and 30% forms was prepared and used during the experiments.

Patients

The wastes of rosacea patients' diagnostic SSSB samples from two different outpatient clinics were used for the experiments. Specimens demonstrating live *Demodex* mites were selected. The authors excluded the *Demodex* mites in their early life cycle due to their increased susceptibility to therapeutic agents. Considering that parasite viability may differ among specimens with different inclusion time points, the authors evaluated the presence of *Demodex* mites during an average duration of 30-45 seconds in all of the experiments. Afterward, the most active *Demodex* mite was determined as the target and the treatment agents were immediately applied. The study agents were directly injected onto the *Demodex* mites. The movements of the mites were continuously observed via the screen of a digital microscope.

Experimental Design

The study included five experimental groups. Twenty *Demodex* mites were included in each group and 10% azelaic acid, 20% azelaic acid, 30% azelaic acid, or 5% permethrin was applied. In the control group, the movements of the mites were observed after dripping only immersion oil.

Although immersion oil is essential for a detailed examination of mite movements and morphological features when examining SSSB samples, the authors, in their previous observations, found that immersion oil might also reduce the penetration of treatment agents. For this reason, all of the samples included in the study were first scanned at 10× and 40× magnification without dripping immersion oil and roughly evaluated for the presence of *Demodex* mites. The eligible SSSB samples were exposed to treatment agents prepared in either immersion oil or the oily solutions of active treatment agents to enable clear field monitoring at large magnification. The samples were evaluated with a digital microscope (Bresser Optics, Digital LCD Microscope, Germany) with 40× optical zoom to 1600× digital zoom magnification (**Figure 1**). The authors determined the most mobile *Demodex* mite the target in each sample and the monitoring area was fixed to this region. Vitality was assessed by our recently defined method, i.e., the continuous observation of this site on the digital screen for the movement of *Demodex* body and legs, up to a maximum of 240 minutes (23). The authors defined the survival time (ST) of *Demodex* mites as the interval (min) between the first exposure of the mites to the working solution and when their motility ceased. Cessation of movement was defined as the complete absence of trunk and limb movements for 60 seconds. The authors did not apply any manipulation to the mites during the experiments. The mean ST was compared between the five study groups to evaluate the potential in vitro *Demodex* killing activities. Furthermore, observations on the morphological appearance of the *Demodex* mites were recorded and assessed during this period.

Statistical Analysis

The exposure of live *Demodex* mites to each study solution was repeated twenty times on independent occasions. Statistical analyses were performed using IBM SPSS for Windows, Version 22.0. Numerical variables were shown as mean±SD. Differences between the groups were evaluated by a two-tailed t-test. A p-value <.05 was considered significant in all comparisons.

RESULTS

All of the mites included in the study were *Demodex folliculorum*. The study did not include *Demodex* brevis mites, which were rarely observed in SSSB samples. All 80 mites exposed to the active treatment solutions except those in the control group (immersion oil) were completely free of movement within the first 20 minutes of exposure (min-max: 10-18 minutes). Mean ST was 15.85±1.6, 14.05±1.5, and 12±1.2 minutes in the 10%, 20%, and 30% azelaic acid groups, respectively. The differences between the three groups did not reach statistical significance (p>0.05) (**Table 1**). The mean ST was 12.2±1.5 minutes in the 5% permethrin group. In the comparative evaluation of the permethrin group with the azelaic acid groups, no difference was observed in terms of ST (p>0.05) (**Table 1**). The mean ST of the control group was 197±23.6 minutes.

Figure 1. The digital microscope enabling the continuous observation of *Demodex* movements

Table 1. The mean±SD survival time in the five experimental groups - p values

		5% Permethrin	10% AA	20% AA	30% AA	Negative Control
		12.2±1.5	**15.85±1.6**	**14.05±1.5**	**12±1.2**	**197±23.6**
5% Permethrin	12.2±1.5	-	0.735	0.691	0.168	0.000
10% AA	15.85±1.6	0.735	-	0.449	0.067	0.000
20% AA	14.05±1.5	0.691	0.449	-	0.343	0.000
30% AA	12±1.2	0.168	0.067	0.343	-	0.000
Negative Control	197±23.6	0.000	0.000	0.000	0.000	-

AA: Azelaic acid

Morphological degeneration findings were detected simultaneously with the cessation of movement in all of the mites in the permethrin group. Morphological degeneration consisted of trunk shrinkage and either blunting or a complete loss of claw and nail structures within the extremities of the *Demodex* mites (**Figure 2**). However, the protrusions depicting extremities were still visible on the lateral sites of the mites during later examinations. As an exceptional finding, fragmentation of mites was observed. These mites were also screened after the cessation of movement and the loss of lateral protrusions was a late finding (**Figure 2**). These differences between the early- and late-stage observations suggested the contraction was related to paralysis of the mites.

None of the mites in the azelaic acid or control groups showed any alteration in body integrity or signs of morphological degeneration. The parasites had a linear appearance related to the eversion of the extremities and the loss of lateral protruding structures (**Figure 3**).

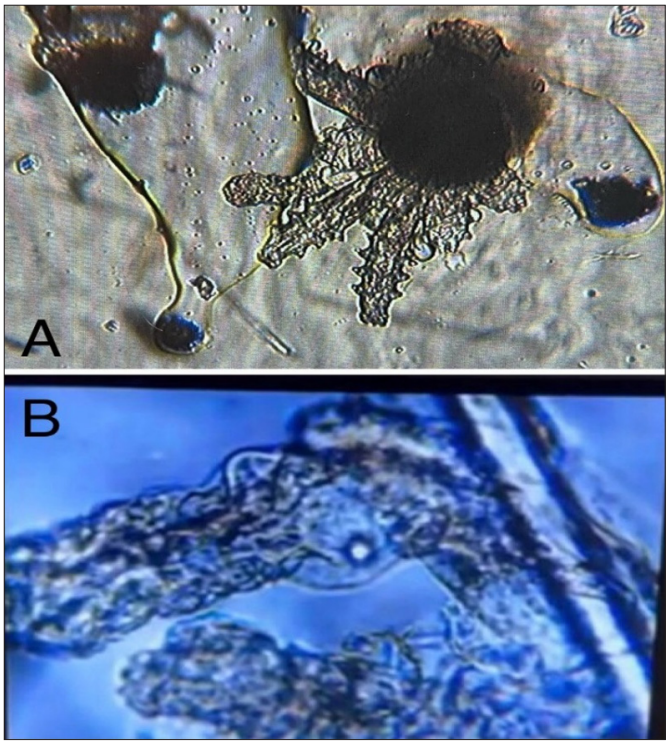

Figure 2. *Demodex* mites in the permethrin group. A) Trunk shrinkage and the loss of delicate features within the limbs. However, the lateral protrusions are prominent, indicating contraction. B) Fragmentation of the trunk and loss of the prominent lateral protrusions

Figure 3: *Demodex* mites in the azelaic acid group. The eversion of the lateral structures led to a linear appearance concurrent with the end of movement.

DISCUSSION

In the current study, by using our recently developed technique, we found that different azelaic acid concentrations had an in vitro anti-*Demodex* efficacy comparable to that of permethrin 5%. Although numerical differences were detected in ST between the different azelaic acid concentrations, these differences did not reach statistical significance. All concentrations of azelaic acid between 10% and 30% provided efficacy similar to that of permethrin 5%. All the active treatment agents had a significant effect on the ST of *Demodex* mites compared to the negative control group.

Although acaricidal agents are frequently incorporated in the management of rosacea with successful treatment outcomes, there is no consensus yet on the optimal dose and treatment duration of these regimens or long-term follow-up results (9). Azelaic acid is a versatile, effective dermatological treatment agent used to treat different cutaneous disorders like melasma, acne, and rosacea related to different action mechanisms (27). *Demodex* mites are sensitive to alterations within their microenvironment. As a typical example, systemic isotretinoin treatment can dramatically decrease *Demodex* density related to the inhibition of sebum production (1). Thus, in clinical practice, several agents can provide decreases in *Demodex* density related to either a direct effect on the mites or an indirect effect related to other changes within the skin. However, instead of an indirect effect related to microenvironmental changes, the results of our study revealed that azelaic acid might have an effect profile similar to that of permethrin on *Demodex* mites, in addition to its well-known antibacterial effects.

In another study, we recently compared the in vitro *Demodex* killing activity of tea tree oil to that of permethrin (23). During the experiments, only the permethrin group had notable findings suggesting morphological degeneration, even fragmentation (23). None of the samples in the tea tree oil groups demonstrated these findings. Thus, the morphological features were also examined in detail in the present study. Upon morphological evaluation of *Demodex* mites, degeneration findings were observed only in the permethrin group. These findings differed between the early stage and late stage. On the other hand, the

morphological features of the azelaic acid groups were identical to those of the negative control group. From this perspective, azelaic acid's *Demodex* killing potential is not identical to that of permethrin and the preservation of the mites' integral structure may prevent the exacerbation of patient-related symptoms.

A common scenario clinicians experience after introducing acaricidal treatment in patients with high *Demodex* density is increased irritation and erythema. The exacerbation of the symptoms may be related to a hypersensitivity reaction to the dead *Demodex* mites. Although typically the intact mites do not evoke an inflammatory response, the fragmentation and degeneration of the mites might cause this exaggerated response (2). This phenomenon is frequently observed with permethrin, a major cause of treatment incompatibilities. Hence, shorter-duration topical applications are often used at the initial stages of permethrin treatment, and the applications are gradually increased. The intense morphological degeneration recorded in the permethrin group may contribute to this situation. The acaricidal effect provided by azelaic acid without this morphological degeneration can represent an advantage to prevent these exacerbations. This prediction needs to be supported by clinical observations and studies on this subject. However, despite being considered a first-line treatment approach for rosacea, azelaic acid can have an irritative potential on the skin independent of *Demodex* mites. Thus, similar to permethrin, rosacea patients with increased *Demodex* mites should be treated with a gradually increasing treatment scheme of azelaic acid.

The findings of the present study are limited to in vitro experiments and do not entirely reflect the efficacy of these agents in clinical practice. Another study limitation is that a dose-dependent response pattern could not be demonstrated for azelaic acid and all three study concentrations had similar effects. The preferences for selecting the drug concentrations were determined according to routine clinical practice. Azelaic acid concentrations below 10% were not included in the study due to the use of 15% azelaic acid in rosacea.

CONCLUSION

In addition to the versatile efficacy of azelaic acid for dermatological diseases, the present study's findings revealed an acaricidal effect similar to that of permethrin 5% on *Demodex folliculorum*. Azelaic acid is a first-line treatment for rosacea. Considering the relationship between rosacea and *Demodex* mites, we think that azelaic acid is also an acceptable agent in rosacea patients with high *Demodex* density and may eliminate the need for additional acaricidal treatments. Azelaic acid can also minimize the possibility of hypersensitivity reactions related to the degeneration of mites. This advantage of azelaic acid may make it preferable to permethrin for cutaneous demodicosis, considering the altered skin barrier of these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The University of Health Sciences Gülhane Scientific Researches Ethics Committee approved the study (Date: 06.01.2022, Decision No: 2022/10).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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REFERENCES

1. Elston CA, Elston DM. *Demodex* mites. Clin Dermatol 2014; 32: 739-43.
2. Lacey N, Raghallaigh SN, Powell FC. *Demodex* mites-commensals, parasites or mutualistic organisms? Dermatology 2011; 222: 128.
3. Chen W, Plewig G. Human demodicosis: revisit and a proposed classification. Brit J Dermatol 2014; 170: 1219-25.
4. Czepita D, Kuźna-Grygiel W, Kosik-Bogacka D. Investigations on the occurrence as well as the role of *Demodex* follicuforum and *Demodex* brevis in the pathogenesis of blepharitis. Klinika Oczna 2005; 107: 80-2.
5. Ivy SP, Mackall CL, Gore L, Gress RE, Hartley AH. Demodicidosis in childhood acute lymphoblastic leukemia: an opportunistic infection occurring with immunosuppression. J Pediatr 1995; 127: 751-4.
6. Aktaş Karabay E, Aksu Çerman A. *Demodex folliculorum* infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis. An Bras Dermatol 2020; 95: 187-93.
7. Chang Y-S, Huang Y-C. Role of *Demodex* mite infestation in rosacea: A systematic review and meta-analysis. J Am Acad Dermatol 2017; 77: 441-7.e6.
8. Forton FMN. The pathogenic role of *Demodex* mites in rosacea: a potential therapeutic target already in erythematotelangiectatic rosacea? Dermatol and Ther 2020: 1-25.
9. Jacob S, VanDaele MA, Brown JN. Treatment of *Demodex*-associated inflammatory skin conditions: a systematic review. Dermatol Ther 2019; 32: e13103.
10. Kligman AM, Christensen MS. *Demodex folliculorum*: requirements for understanding its role in human skin disease. J Invest Dermatol 2011; 131: 8.

11. Lacey N, Russell-Hallinan A, Zouboulis CC, Powell FC. *Demodex* mites modulate sebocyte immune reaction: possible role in the pathogenesis of rosacea. Brit J Dermatol. 2018; 179: 420-30.
12. Aşkın Ü, Seçkin D. Comparison of the two techniques for measurement of the density of *Demodex folliculorum*: standardized skin surface biopsy and direct microscopic examination. Brit J Dermatol 2010; 162: 1124-6.
13. Aytekin S, Göktay F, Yaşar Ş, Gizlenti S. Tips and tricks on *Demodex* density examination by standardized skin surface biopsy. J Eur Acad Dermatol Venereol 2016; 30: e126-e8.
14. Forton F, Seys B. Density of *Demodex folliculorum* in rosacea: a case-control study using standardized skin-surface biopsy. Brit J Dermatol 1993; 128: 650-9.
15. Marks R, Dawber RPR. Skin surface biopsy: an improved technique for the examination of the horny layer. Brit J Dermatol 1971; 84: 117-23.
16. Du J, Gao R, Zhao J. The Effect of Volatile Oil from Chinese Mugwort Leaf on Human Demodecid Mites In Vitro. Acta Parasitol 2021; 66: 615-22.
17. Gao YY, Di Pascuale MA, Li W, et al. In vitro and in vivo killing of ocular *Demodex* by tea tree oil. Brit J Ophthalmol 2005; 89: 1468-73.
18. Jixin L, Chaopin L, Yanhon S, et al. The effect of the volatile oil of Manchurian Wildginger on the killing of *Demodex* in vitro. J Trop Dis Parasitol 2014; 12: 21.
19. Lam NSK, Long XX, Li X, Yang L, Griffin RC, Doery JCG. Comparison of the efficacy of tea tree (Melaleuca alternifolia) oil with other current pharmacological management in human demodicosis: a systematic review. Parasitol 2020; 147: 1587-613.
20. Liu JX, Sun YH, Li CP. Volatile oils of Chinese crude medicines exhibit antiparasitic activity against human *Demodex* with no adverse effects in vivo. Exp Therap Med 2015; 9: 1304-8.
21. Oseka MK, Sedzikowska A. Effect of essential oils on the survival rate of *Demodex* spp. Invest phthalmol Vis Sci 2014; 55: 6252-.
22. Song B, Liu J, Liu T. Effect of galangal essential oil on killing human *Demodex* in vitro. J Path Biol 2010; 5: 155-60.
23. Yurekli A, Botsali A. The comparative in vitro killing activity of tea tree oil versus permethrin on *Demodex folliculorum* of rosacea patients. J Cosmet Dermatol 2022; doi: 10.1111/jocd.14701.
24. Persi A, Rebora A. Metronidazole and *Demodex folliculorum*. Acta Derm Venereol 1981; 61: 182-3.
25. Abokwidir M, Fleischer AB. An emerging treatment: topical ivermectin for papulopustular rosacea. J Dermatol Treat 2015; 26: 379-80.
26. Schulte BC, Wu W, Rosen T. Azelaic acid: evidence-based update on mechanism of action and clinical application. J Drugs Dermatol 2015; 14: 964-8.
27. Searle T, Ali FR, Al-Niaimi F. The versatility of azelaic acid in dermatology. J Dermatol Treat 2020: 1-11.
28. Gollnick H, Layton A. Azelaic acid 15% gel in the treatment of rosacea. Exp Opin Pharmacother. 2008; 9: 2699-706.

Original Article

HEALTH SCIENCES
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Is there any difference between shaving versus clipping versus depilatory gel of hair removal for skin preparation before surgery in respect of wound infection?

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ABSTRACT

Aim: Postoperative wound infection is still the most developing complication after surgery and globally responsible for almost %25 hospitalizations requiring complications after surgery. Several significant parameters to minimize Surgical Site Infection (SSI) evaluated and published in many articles, reviews, and guidelines. We aim to investigate the SSI outcomes of 3 different hair removal procedures before surgery, including skin preparation, in this original research article.

Material and Method: 314 patients enrolled in this study were males aged 18 and 65, admitted to the outpatient clinic with unilateral inguinal hernia, and were eligible for Lichtenstein tension-free open hernia repair using mesh.

Results: Wound infection has occurred in 6 patients from Group-1 (4.83%), 8 patients on Group-2 (7.92%), 4 patients on Group-3 (4.49%). There are no statistically significant between Group1 and Group-3 ($p>0.05$) when the wound infection rates of Group-2 statistically significantly higher than Group-1 and Group-3 ($p<0.05$).

Conclusion: In the light of our study, we suggest either clipping on the table or usage of depilatory gels to maintain hair removal, including preoperative skin preparation.

Keywords: Surgical site infection, hair removal, hernie

INTRODUCTION

Postoperative wound infection is still the most developing complication after any kind of surgery and globally responsible for almost %25 hospitalizations requiring complication after surgery (1-3). The occurrence of a surgical site infection(SSI) leads to cost-effective charges, elongated hospitalization, and even mortality, especially on immunocompromised patients (4,5).

The effect of hair removal at the surgical site on SSI rates is unknown (6). Apart from the groups that recommend not removing hair, some groups remain neutral on this issue or advocate the need for hair removal (7,8). Several significant parameters to minimize SSI were evaluated and published on many articles, reviews, and guidelines (1,8-11). In this original research article, our aim is to investigate the SSI outcomes of 3 different procedures for hair removal before surgery, including skin preparation.

MATERIAL AND METHOD

Ethical approval was obtained from the Hitit University Non-interventional Research Ethics Committee (Date: 01.11.2021, Decision No: 2021-81). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This is a retrospective study aiming to inference the results of 3 different methods of preoperative hair removal after Lichtenstein tension-free open hernia repair with prolene mesh. 314 patients enrolled in this study who were male aged between 18 and 65, who admitted to the outpatient clinic with unilateral inguinal hernia and were eligible.

Inguinal hernia patients may require emergency surgery (12). These patients were excluded from the study because hair cleaning could not be performed. Patients excluded from the study who had scrotal, incarcerated ischemic or necrotic bowel tissue, perforation/infection, or femoral hernia; and prior laparoscopic/open inguinal hernia repair. Inguinal hernia patients may require emergency surgery.

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Preoperative Hair Removal

Group-1: Hair removal with the clipper on the table immediate before surgery starts by the medical attendant

Group-2: Hair removal by the patient himself at home with a razor by shaving 24 hours before surgery

Group-3: Hair removal by the patient himself at home with depilatory gel 24 hours before surgery

After skin disinfection with povidone iodine and prophylactic antibiotherapy applied (50 mL sterile saline with 1 g intravenous cefazolin), the incision has started centering 1 cm upper and latitude of the inguinal ligament, originated from the pubic bone and reaching out 4-5 cm upper of the midinguinal line. Subcutaneous tissue has passed through pudendalis superficialis and epigastrica superficialis branches of these vessels. The Scarpa fascia is dissected to the aponeurosis of the external oblique muscle, then exposure of the external inguinal ring and inguinal ligament completed. The external oblique aponeurosis incised from external inguinal ring to upper-lateral for 5-6 cm. Nervus ilioinguinalis has been secured from secondary trauma. Skin flaps prepared and context of spermatic cord with cremaster muscles hanged up to ensure the security of these structures and help the exposure of area of herniation. Polypropylene mesh has augmented for herniorrhaphy. The patchy edges of the mesh rasped to maintain the optimal adaptation to the prepared area. The mesh has been fixed with 3.0 polypropylene stitches.

Hemostasis secured and spermatic cord layers and other anatomical structures have closed concordantly with the anatomic plane.

The patients have been assessed in respect of early and late postoperative complications and hernia recurrence.

The Ki-square test has used for statistical analysis was performed by using the software package SPSS 17.0 (IBM Corp. Armonk, NY). A difference with $p<0.05$ was considered statistically significant.

RESULTS

A total of 314 patients diagnosed with a unilateral primary inguinal hernia were included and evaluated retrospectively by the patient records. 124 of 314 had immediate removal by clipper on the table (Group-1); 101 of 314 had hair removal by shaving one day before surgery (Group-2); 89 of 314 had hair removal by depilatory gel one day before surgery (Group-3).

Groups were evaluated by demographic parameters (mean age: 50.8 years ±4.3 vs. 55.1 years ±8.8 vs. 52.5±6.6 years for Group-1, Group-2 and Group-3 respectively ($p>0.05$).

The median duration of operation was 60.9 min ±7.1 on Group-1, the median duration of operation was 55.9 min ±11.4 on Group-2 and 58.7 min ±9.9 on Group-3 ($p>0.05$).

Mean hospital stay for all patients was one day, and no statistically significant difference has detected between groups.

None patients participating in this study suffered any intraoperative or postoperative major complication.

Wound infection has occurred in six patients from Group-1 (4.8%), eight patients on Group-2 (7.92%), four patients on Group-3 (4.49%). There are no statistically significant between Group-1 and Group-3 ($p>0.05$) when the wound infection rates of Group-2 statistically significantly higher than Group-1 and Group-3 ($p>0.05$) (**Table**). The bacteria isolated in all 18 patients with wound infections were gram-positive staphylococci (*S. aureus* in 12 patients, *S. epidermitis* in 6 patients). Superficial wound infection developed in all patients with SSI. Deep wound infection did not develop in any patient.

Superficial wound infection dissolved with basic antibiotherapy of all patients except three patients (2 from Group-2, 1 from Group-1). Three patients had developed wound infection requiring parenteral antibiotherapy, which dissolved after ten days of treatment.

The rate of patients in need of analgesics during the follow-up did not differ significantly ($p>0.05$).

No recurrence has detected in both groups after 9.8 months of follow-up.

Table 1. Demographic characteristic and wound infections

	Group-1 (n=124)	Group-2 (n=101)	Group-3 (n=89)	p value
Age, mean, years	50.8 (4.3)	55.1 (8.8)	52.5 (6.6)	0.856
Duration of operation, median	60.9 (7.1)	55.9 (11.4)	58.7 (9.9)	0.756
Hospital stay, day	1	1	1	
Complications	none	none	none	
Wound infections	6 (4.8%)	8(7.9%)	4 (4.4%)	0.008
Recurrence (after 9.8 months)	none	none	none	

DISCUSSION

One of the most significant quality indices of health is the rate at which hospital diseases spread(13). Preoperative skin preparation is described as the sanitization of microorganisms from the skin at the utmost level. The aim is to minimize colonization of the skin of the surgical area and clearly minimize the SSI rates after surgery (14,15).

Hair removal of the surgical area or surgery has been a very important and principal part of preoperative skin preparation. Besides prevention of infection, hair removal would help the suturation of the skin, cleaning the area after the operation, eases the wound exposure on follow-up, and applying wound dressings. Additionally, hair removal can be considered as the removal of bacterias that colonized on the hair, so it helps to reduce wound infection rates postoperatively (14,15).

On the other hand, for example, on cranial operations, hair removal has also been the major part of preoperative surgical site preparation for both SSI reducing effects and Easing postoperative follow-up and dressing, but some recent investigations suggest that there is an increasing trend to avoid hair removal and again some other studies suggest there is no statistically significant difference on SSI development related with hair removal (16-19).

On the contrary, a recent consensus statement of Orthopedics Research Society resulted in the suggestion of hair removal with a strong consensus of 92% suggesting clipper method for hair removal (20).

We designed this retrospective study from this point of view to aim whether hair removal itself or different techniques of hair removal could affect the development of SSI.

It is suggested that hair removal with shaving 24 hours before surgery leads to minor abrasions, which form a ideal environment for bacterial overgrowth and may lead to increase postoperative SSI instead of minimizing (21), on the other hand, if shaving is the only option, it is important to perform immediately before surgery on tablet o avoid bacterial colonization in those micro-exfoliated skin parts (22-24).

Upon immediate shaving is not feasible at busy surgical centers, depilatory gels are to suggest feasible as a broad using cosmetic product (22-26). Depilatory gels may be a good option for shaving if applied appropriately with a user manual to prevent these micro-exfoliations of skin and a very feasible option to apply the areas which are not easy to reach and clean properly (24,27).

Seropian et al. (28) in their study comparing the application of razor and depilatory cream, showed that the infection rates were higher in the application of razors (5.6% and 0.6%, respectively). Similarly, in another study, the infection rate was reported as 10.4% in patients who shaved with a razor. In the same study, the infection rate in the application of depilatory cream was found to be 3.9% (29). These results were supported by seven randomized controlled trials comparing razor and cream hair removal in a meta-analysis. There were a total of 1420 patients in these seven studies. While the infection rate was 10% in patients who shaved with a razor, the infection rate was 7% in patients who were applied epilation cream. However, no statistical difference was found between the groups as a result of the meta-analysis (30).

Although depilatory cream reduces postoperative wound infection rates, it has been suggested that patient-related factors may contribute to wound infection (endogenous and exogenous) as well as preoperative epilation method. In our study, there was the highest rate of wound infection after preoperative razor blade use. Depilation with depilatory cream has been adequately done so that the incidence of skin injuries and skin reactions is much lower, and the high rate of postoperative wound infection that accompanies skin injuries caused by razor shaving can be minimized by the use of depilatory creams. Skin injuries from razor shaving are known to be impacted by the quality of the personnel, but several studies have demonstrated that even skilled shaving can cause injuries, particularly in body crevices, over scars and other skin problems, and in an agitated patient (28).

Our study has limitations. Although being retrospective is the most important limitation, the short follow-up period can also be counted as a limitation. The other limitation of our study was that subgroup analyzes were not performed for markers that would affect the wound. It was from a single center and was overwhelmingly white. We did not collect data about patient feedback or any adverse events that may have been related to study group assignments other than SSIs. The fact that it is a big, contemporaneous, and properly implemented clinical trial is one of the study's merits. The study's pragmatic design and implementation closely resemble real-world practice, making it more generalizable to various surgical populations.

CONCLUSION

The results of our study showed that depilatory gels are a very good alternative to clipping on-table and very promising to be easily applied, simple and non-abrasive aspects. On the contrary, shaving, especially 24 hours before surgery, has been found very associative with significantly higher rates of postoperative SSI development. In the light of our study, we suggest either clipping on the table or usage of depilatory gels to maintain hair removal, including preoperative skin preparation.

There is no person/organization supporting the work financially and the authors have no relationship based on self-interest.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Hitit University Non-interventional Research Ethics Committee (Date: 01.11.2021, Decision No: 2021-81).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Badia JM, Rubio-Pérez I, López-Menéndez J, et al. Spanish Observatory of Surgical Infection. The persistent breach between evidence and practice in the prevention of surgical site infection. Qualitative study. Int J Surg 2020; 82: 231-9.
2. Suetens C, Latour K, Karki T, et al. The Healthcare-Associated Infections Prevalence Study Group, Members of the Healthcare-Associated Infections Prevalence Study Group. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017, Euro Surveill 2018; 23: 1800516.
3. Badia JM, Casey AL, Petrosillo N, Hudson PM, Mitchell SA, Crosby C. Impact of surgical site infection on healthcare costs and patient outcomes: a systematic review in six European countries, J Hosp Infect 2017; 96: 1–15.
4. De Lissovoy G, Fraeman K, Hutchins V, Murphy D, Song D, Vaughn BB. Surgical site infection: incidence and impact on hospital utilization and treatment costs. Am J Infect Control 2009; 37: 387-97.
5. Keenan JE, Speicher PJ, Thacker JK, Walter M, Kuchibhatla M, Mantyh CR. The preventive surgical site infection bundle in colorectal surgery: an effective approach to surgical site infection reduction and health care cost savings. JAMA Surg 2014; 149: 1045-52.
6. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR, Committee HICPA. Guideline for prevention of surgical site infection, 1999. Infect Control Hosp Epidemiol 1999; 20: 247-80.
7. Kowalski TJ, Kothari SN, Mathiason MA, Borgert AJ. Impact of hair removal on surgical site infection rates: a prospective randomized noninferiority trial. J Am Coll Surg 2016; 223: 704-11.
8. Lohsiriwat V, Chinswangwatanakul V, Lohsiriwat D, et al. Guidelines for the prevention of surgical site infection: The Surgical Infection Society of Thailand recommendations (Executive summary). J Med Assoc Thai J Med Assoc Thai 2020; 103: 99-105.
9. Hranjec T, Swenson BR, Sawyer RG. Surgical site infection prevention: how we do it. Surg Infect 2010; 11: 289-94.
10. Tanner J, Khan D. Surgical site infection, preoperative body washing and hair removal. J Perioper Pract 2008; 18: 232-43.
11. Lefebvre A, Saliou P, Lucet J, et al. Preoperative hair removal and surgical site infections: network meta-analysis of randomized controlled trials. J Hosp Infect 2015; 91: 100-8.
12. Topcu R, Yıldırım MB, Özkan MB, Aslan O, Sezikli İ, Şahin F. The effect of COVID-19 pandemic on inguinal hernia emergencies. J Health Sci Med 2021; 4: 865-70.
13. Temoçin F, Hatice K, Sürel AA. Enfeksiyon kontrol önlemlerine ilişkin klinik karar destek sistemlerinin hazırlanması ve etkililiğin değerlendirilmesi. J Health Sci Med 2019; 2: 54-7.
14. Karegoudar JS, Prabhakar PJ, Vijayanath V, Anitha MR, Surpur RR, Patil VM. Shaving versus depilation cream for pre-operative skin preparation. Indian J Surg 2012; 74: 294-7.
15. Markström I, Bjerså K. Diversities in perceived knowledge and practice of preoperative skin preparation in Swedish orthopaedic surgery. J Perioper Pract 2015; 25: 101-6.
16. Lee YH, Kwon YS, Cho JM. Ventriculoperitoneal shunt without hair shaving using absorbable suture materials. J Korean Neurosurg Soc 2021; 64: 120-4.
17. Bhatti MI, Leach PA. The incidence of infection for adults undergoing supra-tentorial craniotomy for tumours without hair removal. Br J Neurosurg 2013; 27: 218-20.
18. Adeleye AO. Nonshaved cranial surgery in black Africans: technical report and a medium-term prospective outcome study. Neurosurg Rev 2016; 39: 449-54.
19. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 2012; 367: 2471-81.
20. Tokarski AT, Blaha D, Mont MA, et al. Perioperative skin preparation. J Orthop Res 2014; 32: 26-30.
21. Boisson M, Corbi P, Kerforne T, et al. Multicentre, open-label, randomised, controlled clinical trial comparing 2% chlorhexidine-70% isopropanol and 5% povidone iodine-69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol. BMJ Open 2019; 9: e026929.
22. Powis SJ, Waterworth TA, Arkell DG. Preoperative skin preparation: clinical evaluation of depilatory cream. Br Med J 1976; 2: 1166-8.
23. Weinstein RA. Epidemiology and control of nosocomial infections in adult intensive care units. The Am J Med 1991; 91: 179-84.
24. Thur de Koos P, McComas B. Shaving versus skin depilatory cream for preoperative skin preparation: A prospective study of wound infection rates. Am J Surg 1983; 145: 377-8.
25. Hu P, Shen H, Wang G, Zhang P, Liu Q, Du J. Prognostic significance of systemic inflammation-based lymphocyte-monocyte ratio in patients with lung cancer: based on a large cohort study. PloS One 2014; 9: e108062.
26. Hu P, Uhlich R, Bosarge PL. Prevention of postoperative infection. Sci Am 2017; 8: 17.
27. Ban KA, Minei JP, Laronga C, et al. Executive summary of the American College of Surgeons/Surgical Infection Society surgical site infection guidelines—2016 update. Surg Infect 2017; 18: 379-82.
28. Seropian R, Reynolds BM. Wound infection after preoperative depilation versus razor preparation. Am J Surg 1970; 12: 251-4.
29. Court-Brown CM. Preoperative skin depilation and its effect on postoperative wound infections. J Royal Col Surg Edinb 1981; 26: 238-41.
30. Tanner J, Woodings D, Moncaster K. Preoperative hair removal to reduce surgical site infection. Journal of perioperative practice, 2007; 17: 118-32.

Original Article

HEALTH SCIENCES
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Comparison of self-tapping and self-drilling screws in open reduction of mandible fracture

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ABSTRACT

Objective: The purpose of this study is to assess the early postoperative stability of screw systems with mini plates in the treatment of open reduction mandibular angulus fractures.

Material and Method: This study consisted of 3 groups of mini plate or screw fixation: a 1.6 mm diameter drill for Group 1, a 1.2 mm diameter drill for Group 2, and self-drilling screws without drilling in Group 3. We used 9 hemimandibles, 9 plates, and 36 screws in each group. We compared the self-tapping and self-drilling screw systems while maintaining the plate system constant. We generated angulus fractures in 27 hemimandibles taken from 14 sheep mandibles. We separated the samples into 3 groups, each with 9 hemimandibles. All the screws used in the study were 2 mm in diameter and 5 mm in length. We used the servo hydraulic test unit to apply force to the hemimandibles. We applied forces of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, and 150 N to the hemimandibles and recorded the resulting displacements. Data were analyzed with IBM SPSS V23, and conformity to normal distribution was evaluated by the Shapiro-Wilk test.

Results: There was no difference between the groups in terms of the amount of displacement that occurred as a result of the applied forces.

Conclusion: In the treatment of mandibular fractures with open reduction, surgeons should focus on plate-related parameters rather than self-drilling and self-tapping of screws, or drill diameter.

Keywords: Self-drilling screw, self-tapping screw, mandible fracture, open reduction

INTRODUCTION

Traumas of the maxillofacial complex are prevalent health problems and require attention (1,2). Among these injuries, mandible fractures are the most common facial skeletal injuries (3). Mandible fractures are twice as prevalent as midface fractures, accounting for the majority of injuries presented to oral and maxillofacial surgeons (3,4). By localization, mandibular fractures are classified as symphysis, parasymphysis, corpus, angulus, ramus, condylar process, coronoid process, and alveolar process fractures. Mandibular fractures in the angulus region are the second most frequent type with the second highest complication rate, after condylar process fractures (5-7). When the fracture segments of a mandibular angulus fracture are directed upwards, downwards, or posteriorly, the segments may show displacement with muscle straining. In the treatment of angulus fractures, the open reduction and internal fixation approaches offer the basic conditions for functional jaw motions with proper occlusion (8). Today, mini-plate and screw systems are routinely used among open reduction and internal fixation methods in the treatment of such fractures (9,10). Functionally stable fixation (Champy technique) and maximum rigid fixation have been the focus of interest among maxillofacial surgeons (11,12). In the Champy technique, the ideal osteosynthesis site for the angulus region is the external oblique ridge (12). Various combinations of monocortical screws and plates are used for the fixation of angulus fractures (13). Only the outer cortex of the bone is screwed with mini-plates of varied lengths and numbers of holes. For stable fixation, a four-hole mini-plate with two screws on either side of the fracture is usually sufficient. The Champy technique is gradually becoming the standard choice for the treatment of mandibular angulus fractures. Monocortical screws are used in this technique to avoid injuring the tooth roots or the alveolar nerve.

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Self-tapping screws are commonly utilized in the open reduction of mandible fractures after drilling a pilot hole with the maximum screw diameter. Pre-drilling is a standard process in the self-tapping system, but it has drawbacks, including the danger of drill damage to nerves and tooth roots, a loose screw fit, and thermal necrosis of the bone, owing to drilling (14). Self-drilling screws, on the other hand, have a simple wood screw geometry and do not require a pilot hole (15). Self-drilling screws can be placed without drilling the bone because they contain sharp ends and threads that follow an axis of rotation all the way up to the screw head (16). Self-drilling screws can be utilized without a problem for up to 2-mm-thick bones, but in thicker bones, the danger of screw breaking increases (17).

Throughout our usual clinical practice, we noticed that self-drilling screws fit more tightly. We undertook this research to see if self-drilling screw systems provide an advantage over self-tapping screw systems in the open reduction of mandible fractures. The hypothesis of this research is that mini-plate screw systems applied with self-drilling screws and self-tapping screws after 1.2 mm drilling will show less displacement compared to mini-plate systems applied with self-tapping screws after 1.6 mm drilling. We could not discover any studies testing the use of self-drilling screws in an open mandibular reduction in our literature search. In this regard, our research is the first in the literature.

MATERIAL AND METHOD

We used 14 sheep mandibles from 9-11-month-old sheep bred in similar conditions. We separated them from their midlines after cleaning the soft tissues on their surfaces and obtained 28 hemimandibles. To avoid problems in the placement of the experimental setup and the findings of the biomechanical tests, we cut the front section of the mental foramen. We kept the hemimandibles in a humidified freezer at -15°C until all the tests were finished. We created a 1 cm fracture with an electric jigsaw in front of the most concave point of the ascending ramus, at an angle of -45 degrees with respect to the occlusal plane. We determined the fracture lines with a fixed pencil.

Procedures with dead animal or tissue, slaughterhouse materials, waste fetuses are not subject to HADYEK permission.

There were 3 groups in our study, each with 9 hemimandibles. In all three groups, we used a 1-mm-thick, 4-hole, 9-mm-spaced flat titanium mini-plate (Trimed, Turkey).

Group 1: For this group, we drilled holes in the bone with a 1.6 mm diameter drill and fixed it using 4 titanium self-tapping screws (Trimed, Turkey) with a diameter of 2.0 mm and a length of 5.0 mm.

Group 2: For this group, we drilled holes in the bone with a 1.2 mm diameter drill and fixed it using 4 titanium self-tapping screws with a diameter of 2.0 mm and a length of 5.0 mm (Trimed, Turkey).

Group 3: For the last group, we fixed the bones using 4 titanium self-drilling screws with a diameter of 2.0 mm and a length of 5.0 mm (Trimed, Turkey) without drilling into the bone.

We marked and standardized the place where the mini-plates would be located in the regions defined by Champy (in the buccal cortex of the external oblique edge) (12). We used a drill to open the screw holes with a physiodispenser and continual irrigation during the self-tapping screw fixation process. All screws were placed by the same surgeon. To prevent degradation, we kept the hemimandibles in saline water during the fixation process. All procedures, including artificial fracture generation, fixation, and use of servo hydraulic device, were completed within 24 hours.

We built a specially designed steel platform for the experiment. In the mandibular notch regions, we drilled an appropriate hole to fix the hemimandibles to the experimental platform, which was then put on support from the angulus region. We emulated the TME by inserting a horizontal bar through this hole in the notch region. We simulated a pterygomasseteric sling by placing the hemimandible on an abutment from the angulus region. We fixed the 3rd point anteriorly from the mental region. We then placed the hemimandibles on the experimental platform with the occlusal plane parallel to the ground, placing this setup on the servo hydraulic testing device (MTS Criterion: Model 42) and preparing it for loading over the molar teeth (**Figure 1**). The servo hydraulic tester performed a linear, non-cyclic displacement at a rate of 1 mm/s. We first calibrated the device at 10 N force, then increased the force up to 150 N. We recorded the displacement values for every 10 N increase in force.

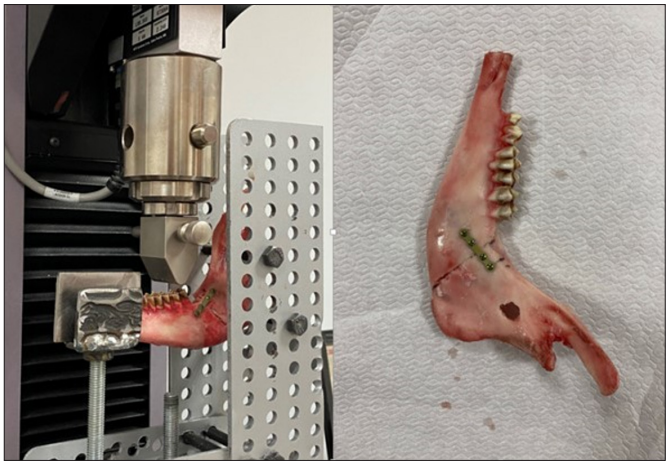

Figure 1. Servo hydraulic tester and the hemimandible prepared for the test

Statistical Analysis

The data were analyzed using IBM SPSS V23. Conformity to normal distribution was evaluated by the Shapiro-Wilk test. To compare displacement measures between groups, we used a one-way analysis of variance and presented the data as mean±standard deviation. Level of significance was taken as $p<0.05$.

RESULTS

None of the study models failed during testing and all met the biomechanical criteria. The **table** below shows the mean and standard deviation of the displacement values of the 3 groups under various forces. In general, as the amount of force increased, the displacement values increased in all groups.

Table. Comparisons by groups

	Self-Drilling	Self-Tapping 1.2 mm	Self-Tapping 1.6 mm	Test ist.[1]	p
	mean±SD	mean±SD	mean±SD		
Displacement at 30N (mm)	0.683±0.561	0.684±0.479	0.562±0.358	0.197	0.823
Displacement at 60N (mm)	1.201±0.95	1.063±0.607	0.836±0.394	0.643	0.535
Displacement at 90N (mm)	1.474±1.008	1.399±0.564	1.079±0.437	0.777	0.471
Displacement at 120N (mm)	1.719±1.022	1.804±0.734	1.391±0.546	0.682	0.515
Displacement at 150N (mm)	1.993±1.054	2.232±1.117	1.704±0.663	0.675	0.519

[1]One-way analysis of variance, SD: standard deviation

Some of the displacement values did not differ between the groups at certain forces; these were 30N (mm) (p=0.823), 60N (mm) (p=0.535), 90N (mm) (p=0.471), 120N (mm) (p=0.515), and 150N (mm) (p=0.519).

Figure 2 shows the mean displacement values for all groups. We found no significant difference between the groups and the amount of displacement increased as the amount of force increased.

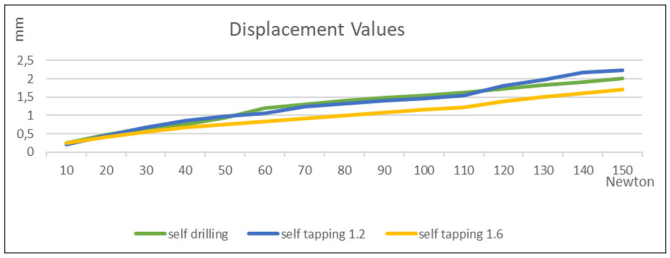

Figure 2. Mean displacement-force graph

DISCUSSION

We used sheep mandibles to compare the early postoperative stability of screw systems in mini-plates used in the treatment of mandible angulus fractures with open reduction. According to our results, we found no difference between the groups, therefore not confirming our hypothesis. The sheep mandible was chosen because it has a Haversian system that is comparable to the human mandible, and it is physically, structurally, and anatomically similar to the human mandible (18). Furthermore, the structural qualities of the bone are intact when used fresh rather than fixed (19,20).

Despite being the largest and strongest of the facial bones, the mandible is broken two to three times more frequently than the other facial bones (1,21). Angulus fractures are the most common of all mandible fractures (5,22,23). Although there are many studies on the treatment of mandibular angulus fractures, no consensus has been established on the best treatment strategy, and research into the ideal treatment method is still ongoing (24). These techniques often involve fixing the bone segments at the lower border of the mandible using a single mini-plate fixation, two mini-plate fixations, bicortical screw applications, or a single reconstruction plate, depending on the case. Among these, the Champy technique is the most widely accepted (12,25). Gear et al. (26) report that single mini-plate treatment has become more popular for mandibular angulus fractures. The use of non-compression, single mini-plate, and monocortical screw fixation on the upper border of the mandible offers less complication rates, according to the general approach to fixation of mandibular angulus fractures (27-32). We designed our study based on this treatment modality adopted by many surgeons.

Gerlach et al. (33) examined bite forces for the molar teeth in patients with fractures of the mandibular angulus treated with mini-plate osteosynthesis and found forces of 90 N at the first week and 148 N at the sixth week. We measured the amount of displacement caused by a 10 N increase in bite force, up to 150 N. Heidemann et al. (34) report that the torque applied during screw insertion increases as the drill diameter used in self-tapping screws decreases. Because self-drilling screws involve no drilling, additional force is needed. We compared self-drilling screws with 1.2 mm and 1.6 mm drills to self-tapping screws without drilling, while maintaining the plate system fixed.

There was no difference between the three groups. Out literature review yielded no study comparing displacement against tensile forces among self-drilling and self-tapping screws. In 1998 , Heidemann et al. (34) investigated the torques and tensile forces of self-drilling and self-tapping screws in polyvinylchloride, wood, and pig mandibular bones. The authors observed different torques in each group and found a difference in displacement against tensile forces in 2 mm thick bone in the mandibular

cortex, although no difference in the 3 mm thick cortical bone (34). Sancar et al. (35) found that cortex thickness was greater than 2 mm in the angulus region posterior to the mandible. We examined the amount of displacement among self-drilling and self-tapping screws against occlusal forces in sheep mandible, which is very similar to the human mandible. In mini-plate screw systems used in the treatment of mandibular fractures, we observed a decrease in the amount of displacement against the occlusal forces by strengthening the drill area where the self-tapping screws are placed (36). In our study, we used 2 mm diameter screws. In our experiments, there was no difference in movement following tensile forces for self-tapping screws after drillings equivalent to 60% (1.2 mm) and 80% (1.6 mm) of the screw diameter. Research has shown that increasing the size of the pilot drill up to 85% of the screw diameter has no effect on the movement caused by tensile forces, as reported by Heidemann et al. (34). These findings are consistent with our results.

CONCLUSION

During the fixation of the jaws with mini-plate screws, the opinion among surgeons is that the tighter the screws are, the stronger the fixation will be. However, our study has demonstrated that this is not the case. Thus, in the treatment of mandible fractures, surgeons should focus on plate-related parameters rather than self-drilling, self-tapping screws, or drill diameter.

ETHICAL DECLARATIONS

Ethics Committee Approval: Procedures with dead animal or tissue, slaughterhouse materials, waste fetuses are not subject to HADYEK permission.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Haug RH, Prather J, Indresano AT. An epidemiologic survey of facial fractures and concomitant injuries. J Oral Maxillofac Surg 1990; 48: 926-32.
2. Adeyemo WL, Iwegbu IO, Bello SA, et al. Management of mandibular fractures in a developing country: a review of 314 cases from two urban centers in Nigeria. World J Surg 2008; 32: 2631-5.
3. Sakr K, Farag IA, Zeitoun IM. Review of 509 mandibular fractures treated at the University Hospital, Alexandria, Egypt. Br J Oral Maxillofac Surg 2006; 44: 107-11.
4. Motamedi MHK. An assessment of maxillofacial fractures: a 5-year study of 237 patients. J Oral Maxillofac Surg 2003; 61: 61-4.
5. Chuong R, Donoff RB, Guralnick WC. A retrospective analysis of 327 mandibular fractures. J Oral Maxillofac Surg 1983; 41: 305-9.
6. Ellis III E. Treatment methods for fractures of the mandibular angle. Int J Oral Maxillofac Surg 1999; 28: 243-52.
7. Schierle HP, Schmelzeisen R, Rahn B, Pytlik C. One-or two-plate fixation of mandibular angle fractures? J Cranıo Maxıll Surg 1997; 25: 162-8.
8. Olate S, Assis AF, Pozzer L, Cavalieri-Pereira L, Asprino L, Moraes M. Pattern and treatment of mandible body fracture. Int J Burns Travma 2013; 3: 164.
9. Iatrou I, Samaras C, Theologie-Lygidakis N. Miniplate osteosynthesis for fractures of the edentulous mandible: a clinical study 1989–96. J Cranıo Maxıll Surg 1998; 26: 400-4.
10. Sauerbier S, Schön R, Otten JE, Schmelzeisen R, Gutwald R. The development of plate osteosynthesis for the treatment of fractures of the mandibular body–A literature review. J Cranıo Maxıll Surg 2008; 36: 251-9.
11. Van Sickels JE, Cunningham LL. Management of atrophic mandible fractures: are bone grafts necessary? J Oral Maxillofac Surg 2010; 68: 1392-5.
12. Champy M, Lodde JP, Schmitt R, Jaeger JH, Müster D. Mandibular osteosynthesis by miniature screwed plates via a buccal approach. J maxillofac Surg 1978; 6: 14-21.
13. Guimond C, Johnson JV, Marchena JM. Fixation of mandibular angle fractures with a 2.0-mm 3-dimensional curved angle strut plate. J Oral Maxillofac Surg 2005; 63: 209-14.
14. Schortinghuis J, Bos RK, Vissink A. Complications of internal fixation of maxillofacial fractures with microplates. J Oral Maxillofac Surg 1999; 57: 130-4.
15. Son S, Motoyoshi M, Uchida Y, Shimizu N. Comparative study of the primary stability of self-drilling and self-tapping orthodontic miniscrews. Am J Orthod Dentofac 2014; 145: 480-5.
16. Sowden D, Schmitz JP. AO self-drilling and self-tapping screws in rat calvarial bone: an ultrastructural study of the implant interface. J Oral Maxillofac Surg 2002; 60: 294-9.
17. Heidemann W, Terheyden H, Gerlach KL. Analysis of the osseous/metal interface of drill free screws and self-tapping screws. J Cranıo Maxıll Surg 2001; 29: 69-74.
18. Duncan WJ. Sheep mandibular animal models for dental implantology research. 2005; University of Otago.
19. Uckan S, Schwimmer A, Kummer F, Grönberg AM. Effect of the angle of the screw on the stability of the mandibular sagittal split ramus osteotomy: a study in sheep mandibles. Br J Oral Maxillofac Surg 2001; 39: 266-8.
20. Haug RH, Barber JE, Punjabi AP. An in vitro comparison of the effect of number and pattern of positional screws on load resistance. J Oral Maxillofac Surg 1999; 57: 300-8.
21. Subhashraj K, Ramkumar S, Ravindran C. Pattern of mandibular fractures in Chennai, India. Br J Oral Maxillofac Surg 2008; 46: 126-7.
22. Ozyurtseven BT, Karsli ED, Balkanlioglu AC. Evaluation of the relationship between wisdom teeth and mandibular fractures. Med-Science 2021; 10: 835-8.
23. Braasch DC, Abubaker AO. Management of mandibular angle fracture. J Oral Maxillofac Surg 2013; 25: 591-600.
24. Cural Ü, Atalay B, Yildirim MS. Comparison of mechanical stabilization of the mandibular angulus fracture fixation, with titanium plates and screws, resorbable plates and screws, and bone adhesives. J Cranio Maxill Surg 2018; 29: 1780-7.

25. Bohluli B, Mohammadi E, Oskuic IZ, Moharamnejad N. Treatment of mandibular angle fracture: Revision of the basic principles. Chinese J Traumatol 2019; 22: 117-9.
26. Gear AJ, Apasova E, Schmitz JP, Schubert W. Treatment modalities for mandibular angle fractures. J Oral Maxillofac Surg 2005; 63: 655-63.
27. Levy FE, Smith RW, Odland RM, Marentette LJ. Monocortical miniplate fixation of mandibular angle fractures. Arch Otolaryngol 1991; 117: 149-54.
28. Barry CP, Kearns GJ. Superior border plating technique in the management of isolated mandibular angle fractures: a retrospective study of 50 consecutive patients. J Oral Maxillofac Surg 2007; 65: 1544-9.
29. Ellis III E, Walker LR. Treatment of mandibular angle fractures using one noncompression miniplate. J Oral Maxillofac Surg 1996; 54: 864-71.
30. Regev E, Shiff JS, Kiss A, Fialkov JA. Internal fixation of mandibular angle fractures: a meta-analysis. Plast Reconstr Surg 2010; 125: 1753-60.
31. Ellis III E. A prospective study of 3 treatment methods for isolated fractures of the mandibular angle. J Oral Maxillofac Surg 2010; 68: 2743-54.
32. Chrcanovic BR. Fixation of mandibular angle fractures: clinical studies. J Oral Maxillofac Surg 2014; 18: 123-52.
33. Gerlach K, Schwarz A. Bite forces in patients after treatment of mandibular angle fractures with miniplate osteosynthesis according to Champy. Int J Oral Maxillofac Surg 2002; 31: 345-8.
34. Heidemann W, Gerlach KL, Gröbel KH, Köllner HG. Influence of different pilot hole sizes on torque measurements and pullout analysis of osteosynthesis screws. J Cranıo Maxıll Surg 1998; 26: 50-5.
35. Sancar B, Dedeoglu N. Morphometric Analysis of Cleft Lip Palate and Prognathic Mandibles in Relation to Mandibular Canal Course. J Cranıofac Surg 2021; 32: 694-7.
36. Cankaya AB, Kasapoğlu MB, Erdem MA, Kasapoğlu Ç. Effects of polymethylmethacrylate on the stability of screw fixation in mandibular angle fractures: A study on sheep mandibles. Int J Med Sci 2018; 15: 1466.

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COVID-19 pandemic: depression and sleep quality in hemodialysis patients

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ABSTRACT

Introduction: Depression and sleep disturbance are prevalent comorbidities in hemodialysis patients. This study aimed to investigate the relationship between depressive mood, sleep disturbance, and the fear of COVID-19 Scale in hemodialysis patients during the pandemic process.

Material and Method: 116 hemodialysis patients followed up in our clinic and volunteered were included in the study. The socio-demographic characteristics of the patients and the laboratory test results studied in their routine follow-ups were obtained from the file records. Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI), and the Fear of COVID-19 Scale (FCV-19S) were applied through face-to-face interviews.

Results: 116 patients (70 males, 46 females) with a hemodialysis duration of 40 months (13-295) and age of 60.2±13.3 years were included in the study. The patients were divided into two groups according to their PSQI score as good sleeper (PSQI ≤ 5, n=66) and poor sleeper (PSQI >5, n=50). When evaluated by gender 28 (56%) female patients were in the poor sleeper group (p=0.002). Dialysis time was longer, BDI score and FCV-19 scale were higher in the poor sleeper group than the good sleeper group. PSQI score was positively correlated with dialysis time (r=0.259 p=0.005), BDI score (r=0.279 p=0.002), and FCV-19 scale (r=0.304 p=0.001). In the Multiple Logistic Regression analysis established to evaluate the risk factors affecting sleep quality, BDI was determined as an independent risk factor for poor sleep (OR: 1.084, 95%CI [1.021-1.152], p=0.008). Subjects were divided into two groups according to their BDI scores as those with depressive mood (BDI score ≥ 17, n=47) (40.5%) and those without (BDI score < 17, n=69) (59.5%). Thirty-two of the cases with depressive mood were women (68.1%) (p<0.001). There was a female predominance in the depressed patient group. The economic status was worse in the depressed group compared to the non-depressed group, and the PSQI score and FVC-19 scale were higher. In addition, BDI score was positively correlated with age (r=0.225 p =0.015), female gender (r=0.473 p=0.001), poor economic status (r=0.576 p =0.001), FVC-19 scale (r=0.330 p =0.001), while negatively correlated with serum albumin level (r=-0.279 p=0.003) and serum creatinine level (r=-0.2455 p =0.008). In the Multiple Logistic Regression model established, female gender (OR: 7.857, 95%CI [2.463-25.065], p<0.001) and poor economic status (OR: 7.569, 95%CI [2,300-24,908], p=0.001) were determined as independent risk factors for depressive mood.

Conclusion: Nearly half of the patients had sleep disorders and depressive mood. Patients in the depressive mood and poor sleep group had a higher FVC-19 scale. We think it would be beneficial not to ignore the increased frequency of depressive mood and sleep disorders in hemodialysis patients during the COVID-19 pandemic.

Keywords: Depressive mood, sleep disorder, fear of COVID-19 scale, hemodialysis

INTRODUCTION

The novel coronavirus disease (COVID-19) is an infectious disease that causes acute upper and lower respiratory tract disease by the SARS-CoV-2 virus and also affects many tissues such as the heart, digestive system, kidneys, blood, and nervous system (1). Social isolation, fears about the virus, boredom, and insufficient information can cause psychiatric disorders in sensitive individuals during the pandemic (2).

Initiation of hemodialysis treatment in chronic kidney patients causes physical and social changes in their lives, and neuropsychiatric complications develop in individuals over time. Depression is the most common psychological problem in hemodialysis patients and is associated with high mortality (3). Although the depression rate is as high as 60% in some studies, depression in patients may still be overlooked because it overlaps with uremic symptoms such as loss of appetite, sleep disturbance, and fatigue (4).

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Sleep disorders are observed quite frequently, between 20% and 70% in patients with chronic kidney disease (5,6,7). In a comprehensive study, the frequency of sleep disorders was defined as 49% (6). In this study; Comorbid diseases such as depression, pain, pruritus, coronary artery disease, congestive heart failure, peripheral artery disease and diabetes, and high body mass index have been associated with poor sleep (6).

Hemodialysis patients are in the high-risk group regarding COVID-19 infection and complications, as they have advanced age, immunosuppression, and many comorbidities such as cardiovascular disease, hypertension, diabetes, and lung disease (8). In addition, the physical proximity of patients during hemodialysis increases the risk of disease transmission (8). During the pandemic, hemodialysis patients generally face an increased risk of encountering covid-19 after and before entering the arena-type hemodialysis room. We think that this situation experienced by the patients is a risk factor for the development of fear of COVID-19. This study was planned to evaluate how depressive mood and sleep disorders were affected by the pandemic in this patient group.

MATERIAL AND METHOD

The study was conducted in compliance with the criteria of the Helsinki Declaration and it was performed between September 2021 and December 2021 after approval by the Health Sciences University Samsun Training and Research Hospital Ethics Committee (Date: 2021, Decision No: 16/10). Written informed consent was obtained from all participants who participated in this study.

The study included 116 patients (70 male, 46 female) undergoing hemodialysis for at least the last six months, over the age of 18, with no cognitive impairment, followed up in our clinic, aged 60.2±13.3 years and having a dialysis duration of 40 months (13-295). The socio-demographic characteristics of the patients and the laboratory test results studied in their routine follow-up were obtained from the clinical file records. Beck Depression Inventory (BDI), Pittsburg Sleep Quality Index (PSQI), and fear of covid-19 scale (FCV-19 scale) were applied through face-to-face interviews.

Beck Depression Inventory (BDI): It is a 21-item scale developed by Beck in 1961. Each question is scored between 0-3, and a total score is taken between 0-63. The results are interpreted as follows: 0-9- no/minimal depression, 10-16- mild depression, 17-29- moderate depression, and 30-63- severe depression (9). While the BDI Turkish version was being developed, crossover points were evaluated, and it was determined that scores of 17 and above determined 90% of the depression requiring treatment (10). The patients were divided into two groups according to their BDI scores. Patients with a BDI score of 17 and above were considered to have depression, and patients with a BDI score of 16 or less were considered to have no depression.

Pittsburg Sleep Quality Index (PSQI): It is a 19-item, retrospective self-report questionnaire developed by Daniel J. Buysse, designed to measure seven domains assessing sleep quality over the past seven days and sleep disturbances in the past month. Items are 1- sleep quality, 2- sleep latency, 3- sleep duration, 4- sleep efficiency, 5- sleep disturbances, 6- use of sleeping medication, and 7- daytime dysfunction. Component scores range from 0 to 21. > 5 points indicate sleep disturbance (11).

Fear of COVID-19 Scale (FCV-19 scale): It is a scale developed by Ahorsu et al. in 2020, aiming to measure the fear levels of individuals due to COVID-19. The scale is a five-point Likert type and has a single factor structure (1=Strongly agree; 5=Strongly disagree). It consists of seven items. There is no multiple-choice test-oriented item in it. An increase in the score obtained from the scale means an increase in fear of COVID-19. The reliability and validity study of the FCV-19 Scale in Turkey was conducted in 2020 by Ladikli et al. (12).

Statistical Analysis

SPSS 21.0.0.1 for Windows (SPSS; IBM) software was used for the analysis. Data distribution was determined using the Kolmogorov-Smirnov test. The homogeneity of the variables was determined using the one-way ANOVA test of homogeneity of variance. According to data distribution, continuous variables were reported as mean and standard deviation or as median and minimum-maximum. Categorical variables were reported as percentages. T-test or Man Whitney U test was used according to data distribution when comparing changes in laboratory parameters within the groups. The Chi-square test or Fisher's Exact test was used to compare categorical variables between the two groups. Logistic regression (Method: Backward: Conditional) test was used in risk factor analysis. A p-value of < 0.05 was considered statistically significant.

RESULTS

The study included one hundred sixteen patients (70 males, 46 females) with HD duration of 40 (13-295) months and age of 60.2±13.3 years. Socio-demographic characteristics and laboratory parameters of the patients participating in the study are given in **Table 1**.

Table 1. Socio-demographic characteristics and laboratory parameters of 116 patients participating in the study

Variable	Mean±sd (range)
Age±sd, year	60.2±13.3 (23/87)
Gender (F/M) (%)	46/70 (%39.7/%60.3)
Dialysis time, months (median)	40 (13/295)
Marital status (married/single, widowed)(%)	71 (%61.2)/45(%38.8)
Economic status (good/medium, bad)	46/70
Calcium±sd (mg/dL)	8.6±0.7
Phosphorus±sd (mg/dL)	5.3±1.2
Albumin±sd (g/dL)	3.6±0.4
Hemoglobin±sd (g/dL)	10.7±1.3
CRP (median) (mg/L)	7.7 (0.7- 348)
PSQI (median) (min/max)	5 (1-12)
BDI (median) (min/max)	14 (2-34)
FCV-19 scale±sd	16.9±5.6

The patients were divided into two groups according to their PSQI score as good sleeper (PSQI ≤ 5, n=66) and poor sleeper (PSQI >5, n=50).). When evaluated by gender 28 (56%) female patients were in the poor sleeper group (p=0.002) and 48 (72.7%) of the male patients were in the good sleeper group, only 22 (44%) were in the poor sleeper group (**Table 2**). Dialysis time was longer, BDI score and FCV-19 scale were higher in the poor sleeper group than the good sleeper group (**Table 2**). In addition, PSQI score was positively correlated with dialysis time (r=0.259 p=0.005), BDI score (r=0.279 p=0.002), and FCV-19 scale (r=0.304 p=0.001).

Table 2. Comparison of Demographic and Laboratory Data in the good sleeper and poor sleeper patients

	Good Slepers (PSQI ≤ 5, n=66) (56.9%)	Poor Sleepers (PSQI >5, n=50) (43.1%)	P
Age±sd, year	58.8±14.3	62.1±11.8	0.200
Gender (F/M) (%)	18/48	28/22	0.002
Dialysis time, months (median)	34 (13-295)	47.5 (13-224)	0.040
Marital status (married/ single, widowed)(%)	42/24	29/21	0.537
Economic status (good/ medium, bad)	30/36	16/34	0.142
Calcium±sd (mg/dL)	8.8±0.7	8.5±0.6	0.059
Phosphorus±sd (mg/dL)	5.2±1.1	5.3±1.4	0.612
Albumin±sd (g/dL)	3.6±0.4	3.5±0.4	0.431
Hemoglobin±sd (g/dL)	10.6±1.1	10.9±1.3	0.231
CRP (median) (mg/L)	7 (0.7-326)	9 (1.7-348)	0.354
kTv±sd	1.13±0.2	1.15±0.2	0.590
BDI (median)	10 (2-34)	20 (4-34)	0.000
FCV-19 scale±sd	15.6±5	18.6±5.9	0.004

In the Multiple Logistic Regression analysis established to evaluate the risk factors affecting sleep quality, BDI was determined as an independent risk factor for poor sleep (OR: 1.084, 95%CI [1.021-1.152], p=0.008).

Subjects were divided into two groups according to their BDI scores as those with depressive mood (BDI score ≥ 17, n=47) (40.5%) and those without (BDI score < 17, n=69) (59.5%). Thirty-two of the cases with depressive mood were women (68.1%), and 15 were male (31.9%) (p<0.001). **Table 3** gave the depressive and non-depressive groups' socio-demographic, clinical, and laboratory parameters data and comparisons. As a result of the comparison between the two groups, there was a female predominance in the depressed patient group (**Table 3**). The economic status was worse in the depressed group compared to the non-depressed group, and the PSQI score and FVC-19 scale were higher (**Table 3**). In addition, BDI score was positively correlated with age (r=0.225 p =0.015), female gender (r=0.473 p=0.001), poor economic status (r=0.576 p =0.001), FVC-19 scale (r=0.330 p =0.001), while negatively correlated with serum albumin level (r=-0.279 p=0.003) and serum creatinine level (r=-0.2455 p =0.008).

Table 3. Comparison of socio-demographic characteristics and laboratory parameters of depressed and non-depressed patients participating in the study

	Depressive Mood Group (BDI score ≥ 17, n=47) (40.5%)	Non-Depressive Mood Group (BDI score < 17, n=69) (59.5%)	P
Age±sd, year	62.9±11.2	58.3±14.4	0.065
Gender (F/M) (%)	32/15	14/55	0.000
Dialysis time, months (median)	46 (13-295)	13 (34-224)	0.434
Marital status (married/ single, widowed)(%)	29/18	42/27	0.928
Economic status (good/medium, bad)	6/41	40/29	0.000
Calcium±sd (mg/dL)	8.5±0.6	8.7±0.7	0.052
Phosphorus±sd (mg/dL)	5.1±1.3	5.4±1.1	0.141
Albumin±sd (g/dL)	3.5±0.4	3.6±0.4	0.120
Hemoglobin±sd (g/dL)	10.9±1.2	10.7±1.2	0.445
CRP (median) (mg/L)	7.7 (0.7/348)	7.75 (0.9/326)	0.775
kTv±sd	1.15±0.19	1.14±0.23	0.822
PSQI (median)	7 (1/ 12)	4 (1/ 12)	0.822
FCV-19 scale±sd	19.1±5.9	15.4±4.8	0.000

In the Multiple Logistic Regression model established, female gender (OR: 7.857, 95%CI [2.463-25.065], p<0.001) and poor economic status (OR: 7.569, 95%CI [2,300-24,908], p=0.001) were determined as independent risk factors for depressive mood.

DISCUSSION

The mean BDI score of our patients was 14, the PSQI score was 5, and the FCV-19 scale was 16±5.6. 43.1% of the patients had poor sleep, and 40.5% had depressive mood. Higher FCV-19 scale scores were associated with mild to moderate depressive mood and worsening sleep quality.

The coronavirus with high transmission potential (COVID-19), identified in China at the end of 2019, has been recognized as a pandemic by the World Health Organization. Insufficient information about the virus has caused fear in the population, and the situation remains unclear due to the lack of effective treatment in the study by Malta et al. And Ornel et al. (13, 14). It is expected that emotions such as fear and anger will arise due to many unknowns about the SARS-CoV-2 virus. Fear is an essential defense mechanism for survival, but when disproportionate, it can become harmful and even lead to the development of psychiatric disorders. During the pandemic, fear may increase the anxiety level in healthy individuals, so the risk of developing psychiatric disorders in the study by Shigemura et al. (15). Our study determined depressive mood and sleep disorders in nearly half of the hemodialysis patients during the pandemic and associated the FCV-19 scale with depressive mood and poor sleep. In addition, poor sleep was positively correlated with the duration of hemodialysis. This may be due to the higher risk of dying from COVID-19 infection due to increased comorbidity and immunosuppression in hemodialysis patients.

It is known that moderate depressive symptoms are present in 25% of patients with end-stage renal disease and major depression in 5-22% in the study by Cohen et al. (16). The etiology of dialysis-induced depression is multifactorial and is related to biopsychosocial mechanisms in the study by Chilcot et al. (17). While biological mechanisms include increased cytokine levels, genetic predisposition, and neurotransmitters affected by uremia, psychosocial factors include altered family and social relationships by hopelessness, loss, perception of lack of control, and job loss in the study by Chen et al. (18). The COVID-19 pandemic has detrimental effects on the general population's physical, mental and social health, such as fear, frustration, boredom, financial loss, and stress in the study by Brooks et al. (19). In the study by Umucu et al. (20) reported that participants with chronic diseases had moderate levels of stress, depression, and anxiety related to COVID-19. Conducted on hemodialysis patients during the COVID-19 pandemic, depression and sleep quality prevalence were 33.3% and 56.9%, respectively in the study by Naamani et al. (21) and in the study by Merlino et al. (22). We think that the high rate of depressive mood in our study may be related to the SARS-Cov-2 pandemic.

Sleep-related complaints are common in patients with end-stage renal disease. It is stated that the rate of sleep complaints in hemodialysis patients is 45%-80% in the study by Bilgic et al. (23). In this group of patients, sleep disturbance is associated with metabolic changes, itching, bone pain, and low hemoglobin levels (23). Our study found no such relationship between sleep index and hemoglobin, calcium, and phosphorus values. The small sample size may be the reason for this situation. Huang et al. (24) determined the frequency of poor sleep was 18.2% in the general population during the COVID-19 epidemic. Our results also showed that the FCV-19 scale was associated with worsening sleep quality. Due to the increased burden in hemodialysis patients, it is expected that depressive mood and poor sleep have increased after the COVID-19 pandemic.

Besides, it should be considered that sleep problems in hemodialysis patients may be related to psychological factors and metabolic changes in the study by Bilgic et al. (23). As is known, insomnia lowers a person's energy, makes him irritable, and takes all the joy out of life. Poor general condition and decreased appetite due to insomnia are also associated with malnutrition (23). In our study, poor sleepers had a statistically significant higher depression score, and their serum albumin levels were negatively correlated with the depression score. However, no correlation was found between serum albumin levels and sleep scores. The pandemic has placed significant burdens on mental health. The decrease in sleep duration and quality also increases the risk of viral infection in the study by Gamaldo et al. (25), in the study by Xiao et al. (26). The groups most affected by the pandemic are women, those with a history of psychiatric disorders and chronic comorbid diseases in the study by Özdin et al. (27). In our study, depression scores and poor sleep were also associated with the female gender.

A study conducted in Japan stated that the pandemic dramatically affected individuals not only psychiatrically but also economically in the study by Shigemura et al. (15). This study also determined that the economic status of the depressed patient group was poor.

The circadian rhythm facilitates daytime wakefulness and nighttime sleep. Melatonin is a hormone secreted by the pineal gland and exhibits anti-inflammatory, antioxidant, and immunomodulatory properties, and insomnia are more common in hemodialysis patients due to impaired circadian rhythm in the study by Koch et al. (28). Disruption of circadian rhythm increases susceptibility to infection. Chronic stress and sleep deprivation stimulate proinflammatory responses and reduce the levels and activities of protective immune cells in the study by Dhabhar et al. (29) and in the study by Akbulut et al. (30). Quarantine significantly alters sleep-wake rhythms and reduces sleep quality in the study by Akıncı et al. (31). In our study, poor sleep was present in 43.1% of the patients and positively correlated with the FCV-19 scale.

The main limitations of our study were the small sample size, the single-center design, and the use of PSQI to measure sleep quality. There is a need for more comprehensive studies using non-subjective sleep assessment methods such as polysomnography.

CONCLUSION

Most of the our patients had sleep disturbance and depressive mood. Patients in the depressive mood and poor sleeper group had a higher FCV-19 scale. We think it would be beneficial to keep depression and sleep disorders in mind to strengthen the immune system of hemodialysis patients and reduce the burden of disease in the COVID-19 pandemic. Considering the psychological consequences of epidemics as well as the physical effects is essential for the protection of mental health. Therefore, specific strategies should be adopted to deal with depressive mood, sleep disturbance, and fear of covid-19 by working closely with the psychiatric team.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Samsun Training and Research Hospital Ethics Committee (Date: 2021, Decision No: 16/10).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The novel coronavirus 2019 epidemic and kidneys. Kidney Int 2020; 97: 824–8.
2. Xiang Y T, Yang Y, Li W, et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. Lancet Psychiatry 2020; 7: 228–9.
3. Lopes AA, Bragg J, Young E, et al. Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. Kidney Int 2002; 62: 199–207.
4. Watnick S, Kirwin P, Mahnensmith R, Concato J. The prevalence and treatment of depression among patients starting dialysis. Am J Kidney Dis 2003; 41: 105–10.
5. Davison SN, Levin A, Moss AH, et al. Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: developing a roadmap to improving quality care. Kidney Int 2015; 88: 447–59.
6. Elder SJ, Pisoni RL, Akizawa T, et al. Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2008; 23: 998–1004.
7. Lindner AV, Novak M, Bohra M, Mucsi I. Insomnia in patients with chronic kidney disease. Semin Nephrol 2015; 35: 359–72.
8. Ikizler TA. COVID-19 and dialysis units: what do we know now and what should we do? Am J Kidney Dis 2020; 76: 1–3.
9. Richter P, Werner J, Heerlein A, Kraus A, Sauer H. On the validity of the Beck Depression Inventory. A review Psychopathology 1998; 31: 160-8.
10. Hisli N. Beck Depresyon Envanteri'nin geçerliliği üzerine bir çalışma. Psikoloji Derg 1998; 6: 118–22.
11. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. Pittsburgh Uyku Kalitesi İndeksi: Psikiyatrik uygulama ve araştırma için yeni bir araç. Psikiyatri Araş 1989; 28 : 193–213.
12. Ladikli N, Bahadır E, Yumusak F, Akkuzu H, Karaman G, Turkkan Z. Uluslararası Sosyal Bilimler Derg 2020; 3: 71-80.
13. Malta M, Rimoin AW, Strathdee SA. The coronavirus 2019-nCoV epidemic: is hindsight 20/20? E Clin Med 2020; 20: 100289.
14. Ornell F, Schuch BJ, Sordi AO, Kessler FHP. Pandemic fear" and COVID-19: mental health burden and strategies. Braz J Psychiatry 2020; 42: 232-5.
15. Shigemura J, Ursano RJ, Morganstein JC, Kurosawa M, Benedek DM. Public responses to the novel 2019 coronavirus (2019-nCoV) in Japan: mental health consequences and target populations. Psychiatry Clin Neurosci 2020; 74: 281-2.
16. Cohen LM, Dobscha SK, Hails KC, et al. Depression and suicidal ideation in patients who discontinue the life-support treatment of dialysis. Psychosom Med 2002; 64: 889–96.
17. Chilcot J, Wellsted D, Da Silva-Gane M, Farrington K. Depression on dialysis. Nephron Clin Pract 2008; 108: 256-64.
18. Chen CK , Tsai YC, Hsu HJ, et al. Depression and suicide risk in hemodialysis patients with chronic renal failure Psychosomatics Nov-Dec 2010; 51: 528.
19. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020; 395: 912–20.
20. Umucu E, Lee B. Examining the impact of COVID-19 on stress and coping strategies in individuals with disabilities and chronic conditions. Rehabil Psychol 2020; 65: 193–8.
21. Naamani AZ, Gormley K, Noble H, Santin O, Maqbali MA. Fatigue, anxiety, depression and sleep quality in patients undergoing haemodialysis. BMC Nephrol 2021; 22: 157.
22. Merlino G, Piani A, Dolso P, et al. Sleep disorders in patients with end stage renal disease undergoing dialysis therapy. Nephrol Dial Transplant 2006; 21: 184–90.
23. Bilgic A, Akgul A, Sezer S, Arat Z, Ozdemir FN, Haberal M. Nutritional status and depression, sleep disorder, and quality of life in hemodialysis patients. J Ren Nutr 2007; 17: 381-8.
24. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res 2020; 288: 112954.
25. Gamaldo CE, Shaikh AK, McArthur JC. The sleep-immunity relationship. Neurol Clin 2012; 30: 1313–43.
26. Xiao H, Zhang Y, Kong D. Social Capital and sleep quality in individuals who self-isolated for 14 days during the coronavirus disease 2019 (COVID-19) outbreak in January 2020 in China. Med Sci Monit 2020; 26: 921–3.
27. Özdin S, Bayrak Özdin Ş. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: the importance of gender. Int J Soc Psychiatr 2020; 66: 504–11.

28. Koch BC, Nagtegaal JE, Hagen EC, et al. The effects of melatonin on sleep-wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, crossover study (EMSCAP study) Br J Clin Pharmacol 2009; 67: 68–75.
29. Dhabhar F.S. Enhancing versus suppressive effects of stres on immune function: implications for immunoprotection and immunpathology. Neuroimmunomodulation 2009; 16: 300–317.
30. Akbulut H, İçli F, Büyükçelik A. The role of granulocyte-macrophage-colony stimulating factor, cortisol, and melatoninin the regulation of the circadian rhythms of peripheral blood cells in healthy volunteers and patients with breast cancer. J Pineal Res 1999; 26: 1–8.
31. Akıncı T , Başar HM. Relationship between sleep quality and the psychological status of patients hospitalised with COVID-19 Sleep Med 2021; 80: 167-70.

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Preterm placental calcification: maternal calcium, magnesium, 25(OH)D levels and adverse obstetric outcomes in low-risk pregnant women

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ABSTRACT

Aim: The aim of our study is to examine early and late preterm placental calcification (PPC) and compare their relationship with maternal calcium, magnesium and 25(OH) D levels and adverse obstetric outcomes.

Material and Method: This prospective cohort study was conducted by examining the pregnant women at their 24th to 36th gestational weeks who applied to the Gynecology Department of Okmeydani Training and Research Hospital. In this study, 207 patients were selected as the study group.

Results: When the early and late PPC groups were compared, rates of low birth weight (LBW) was statistically higher in the early PPC group. (p=0.022) Oligohydramnios was more common in the early and late PPC patients compared to non-PPC pregnant women. However, oligohydramnios and LBW were not found statistically significant difference in logistic regression analysis. There was also no statistically significant difference in maternal calcium, magnesium and vitamin D levels between the groups.

Conclusion: Preterm placental calcifications might be associated with fetal and maternal complications. But the diagnosis of PPC alone is not effective in determining fetal prognosis.

Keywords: Calcium, low birth weight, magnesium, preterm placental calcification, vitamin D

INTRODUCTION

Placenta acts as a basic endocrine organ while providing nutrient transfer between mother and fetus during pregnancy. Placental calcification (PC) is a condition frequently detected in ultrasonographic examination during pregnancy. The echogenic focus image in the placenta occurs as a result of calcium accumulation in the placental tissue and is generally seen on the maternal aspect and perivillous areas. Possible causes of tissue calcification can be physiological, dystrophic and metastatic (1). When calcium accumulates in the basement membrane and lobules, a linear or lobulated echogenic image is formed. Using the maturational changes in placenta, Grannum et al. created a grading system (2). The indentations and ring formation are seen in Grade III placenta, and they found in 39.4% of pregnany at term (3,4). Calcifications seen before the 36 weeks of gestation are called preterm placental calcifications (PPC) and have been found to be associated with obstetric complications (5). There are studies showing that low birth weight (LBW) and abnormal Doppler ultrasound findings are more frequently seen in this group (6).

Calcium and magnesium have a role in the regulation of myometrial activity and maternal serum levels decrease with advancing gestational weeks (7). In the second trimester, premature uterine contraction in women may be related to the homeostasis of calcium-phosphorus-magnesium (8). Maternal calcium and vitamin 25 (OH) D levels were found to be associated with PC and it was concluded that the placenta is important in vitamin D regulation (9,10).

The aim of our study is to examine PPC and compare their relationship with maternal calcium, magnesium and vitamin D levels and adverse obstetric outcomes.

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MATERIAL AND METHOD

The study was initiated with the approval of the Okmeydanı Training and Researches Hospital Ethics Committee (Date: 23/12/2019, Decision No: 48670771-514.10./1511). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

This prospective cohort study was conducted by examining the pregnant women at their 24th to 36th gestational weeks who applied to the Gynecology Department of Okmeydani Training and Research Hospital and had antenatal follow-ups between January 1,2020 and December 31,2020. Gestational age was calculated according to the last menstrual period or findings of ultrasound performed before the 20th gestational week. Gravida, parity, abortion numbers, maternal height, weight values, gestational week of all patients were recorded. Multiple pregnancy, smokers, alcohol users, pregnant women under 18 years old, those with diagnosed chromosomal anomalies, maternal chronic diseases, asthma, pregestational diabetes, and placenta previa, pregnants receiving calcium, magnesium and vitamin D supplementations were excluded from the study.

From antecubital vein of the mothers, we obtained blood samples and calcium, magnesium and vitamin D levels were measured. Obstetric ultrasound was performed to evaluate the status of placenta. Placental maturity was determined using the Grannum classification: Grade 0: uniform echogenicity with smooth chorionic plate; Grade I: Hyperechoic area or parenchymal calcification and indentations of chorionic plate; Grade II: Occasional hyperechoic areas or basal calcification and deeper indentations of the chorionic plate; Grade III: Basal plate calcification, chorionic plate interrupted by indentations that invate to the basal plate (2). All ultrasonographic examinations were performed by one qualified obstetrician using a Esaote My Lab Seven equipped with a 1–8 MHz convex-arrayabominal transducer to avoid interobserver bias.

Grade III placental calcifications detected at earlier than 36th gestational weeks were recorded as preterm placental calcification (PPC). Patients were followed up until delivery. Although the study started with 246 pregnant women, 207 patients were selected as the study group because birth records of 39 patients were not available. Weeks of delivery, fetal weight, delivery type, cesarean indications and gender of the newborns were recorded. Besides, maternal, and obstetric outcomes as preeclampsia, oligohydramios, polyhydramnios, small for gestational age (SGA), preterm birth, postterm birth, preterm premature rupture of membrane (PPROM), premature rupture of membrane (PROM), low birth weight (LBW), preeclampsia, gestational diabetes mellitus (GDM), mort de fetus, macrosomia were recorded.

According to the time when placental calcification was initially confirmed women were classified into one of three groups as follows: an early PPC (Group 1, n=43), in whom PPC was found prior to 32. gestational week, and a late PPC (Group 2, n=62), in whom PPC was found between 32. and 36. gestational weeks; and a control group (Group 3, n=102), in whom PPC was not seen between 24. and 36. gestational weeks.

Maternal calcium, magnesium, vitamin 25 (OH) D levels, and adverse obstetric outcomes were compared with placental grades. Reference ranges for serum magnesium (1,8-2,6 mg/dl) Vitamin 25(OH)D (20-50 μg) calcium (8.8–10,6 mg/dl) were determined as indicated.

Preterm labor was defined as delivery with cervical dilatation and effacement accompanying with uterine contractions before 37. gestational weeks. Deliveries after 42. gestational week were evaluated as postmature births. Low birth weight was defined as fetal weight of less than 2500 g and fetal macrosomia as over 4000 g. Fetal demise was determined as intrauterine fetal death after 24.weeks of gestation.

In polyhydroamnios, the amount of amniotic fluid is 8 cm above the single quadrant or 20 cm above the sum of four quadrants in ultrasonography. In oligohydramnios, amount is 2 cm below the single quadrant measurement or 5 cm below the total of four quadrants. With the criteria defined by the International Society for the Study of Hypertension in Pregnancy, the diagnosis of gestational hypertension and preeclampsia was made (11). Diagnosis of gestational hypertension was made when blood pressures measured twice at 4 hour intervals were systolic ≥ 140 mmHg, and diastolic ≥ 90 mmHg, in a normotensive pregnant woman who had not significant proteinuria after the 20th gestational week. Diagnosis of preeclampsia was made in consideration of above mentioned findings and also high levels of protein (≥ 300 mg) in 24 hour urine samples or 2 (+) proteinuria at 2 different occasions were detected. As recommended by the American College of Obstetricians and Gynecologists (AGOC), we made the diagnosis of GDM in 2 steps (12). SGA was defined when birth weight below the 10th percentile for gestational age. PROM was defined as rupture of the membranes before the onset of labor. PPROM was defined as spontaneous rupture of the amniotic membrane before the 37. gestational week and the release of amniotic fluid before the onset of labor.

Statistical Evaluation

Using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program, the statistical analyzes were performed. With the Shapiro - Wilk normality test, in the evaluation of the data, descriptive statistical methods (mean, standard deviation, median, interquartile range), the distribution of the variables was examined. Tukey multiple comparison test were used in the intergroup comparisons of variables with normal distribution one-way analysis of variance, and for their subgroup comparisons. Dunn's multiple comparison test were employed for intergroup comparisons of variables without normal distribution Kruskal Wallis test, and for their comparisons of subgroup. For comparisons of qualitative data chi-square test was utilized. To determine the risk factors of early and late PPC groups, logistic regression analysis was performed. The results were evaluated with the significance level of $p < 0.05$.

RESULTS

The demographic characteristics of the women and pregnancy outcomes are shown in **Table 1.** The test week values of the early PPC group were statistically significantly lower than the test week averages of the late PPC and non- PPC groups. (p=0.0001, p=0.012).

The fetal weight of the non-PPC group were found to be statistically significantly lower than the fetal weight values of the late PPC group (p=0.011), but there was no statistically significant difference in fetal weights between the other groups (p> 0.05). There was no statistically significant difference between the early PPC, late PPC and non- PPC groups in terms of mean values for birth weeks, body mass index (BMI), gender distributions (p=0.168, p=0.09, p=0.741 respectively) and calcium, magnesium, vitamin 25 (OH) D levels were not significantly different (p=0,680, p=0,616, p=0,839 respectively).

When the perinatal outcomes were evaluated, there was no statistically significant difference between the groups in terms of preeclampsia, SGA, fetal demise, GDM, oligohydramnios, polyhydramnios, PROM, PPROM, macrosomia, preterm birth, postterm birth and abruptio placenta, while a statistically significant difference was observed between the LBW distributions (p=0.024). When the early and late PPC groups were compared, rates of LBW was statistically higher in the early PPC group. (p=0,022)

Adjusted by maternal age, body mass index, and parity, the analysis was performed by logistic regression to compare the differences in pregnancy outcomes among the three groups, (**Table 2**).

Univariate risk analysis has been made for early PPC, and none of the variables were statistically significant (p> 0.05) regarding preeclampsia (OR, 1.2; 95% CI, 0.28-5.03) LBW (OR, 0.14; 95% CI, 0.007-2.61), SGA (OR, 1.2; 95% CI, 0.29-5.04), GDM (OR, 1.02; 95% CI, 0.25-4.13), oligohydramnios (OR, 3.75; 95% CI, 0.61-13.03), and premature birth (OR, 0.91; 95% CI, 0.30-2,71). Age, parity and BMI were adjusted by performing a multivariate risk analysis with variables with an OR value above 2; and none of the variables were found to be statistically significant.

Univariate risk analysis has been made for late PPC, and none of the variables were statistically significant (p> 0.05) regarding preeclampsia (OR, 1.40; 95% CI, 0.41-4.81), LBW (OR, 2.55; 95% CI, 0.70-9.32), SGA (OR, 0.12; 95% CI, 0.006-2.14), GDM (OR, 0.69; 95% CI, 0.17-2.77), oligohydramnios (OR, 2.54; 95% CI, 0.41-15, 66), premature birth (OR, 0.35; 95% CI, 0.09-1.26)). In addition, in the multivariate risk analysis, none of the variables were found to be statistically significant.

Table 2. Comparison of pregnancy outcome in the study groups

	Group 1		Group 2	
	Univariate Risk	Multivariate Risk	Univariate Risk	Multivariate Risk
	OR (%95 CI)	OR (%95 CI)	OR (%95 CI)	OR (%95 CI)
Preeclampsia	1.2 (0.28-5.03)		1.40 (0.41-4.81)	
LBW	0.14 (0.007-2.61)	0.99 (0.98-1.02) p=0.237	2.55 (0.70-9.32)	1.02 (0.00-1.28) p=0.998
SGA	1.2 (0.29-5.04)		0.12 (0.006-2.14)	
GDM	1.02 (0.25-4.13)		0.69 (0.17-2.77)	
Oligohydramnios	3.75 (0.61-13.03)	1.01 (0.99-1.02) p=0.455	2.54 (0.41-15.66)	0.98 (0.00-1.14) p=0.998
Preterm birth	0.91 (0.30-2.71)		0.35 (0.09-1.26)	

LBW: Low birth weight, SGA: Small for gestational age, GDM: Gestational diabetes mellitus
Group 1, women with early preterm placental calcification (noted at 24-32 week's gestation); Group 2, women with late preterm placental calcification (noted at 32-36 week's gestation); Odds ratios compared to control group (women with no placental calcification noted on ultrasound at 24-36 week's gestation) calculated by logistic regression analysis and adjusted by maternal age, body mass index and parity in multivariate analysis

Table 1. Characteristics and pregnancy outcomes

		Group 1 n:43		Group 2 n:62		Group 3 n:102		p
Age (years)		29.09±5.8		28.71±5.91		29.98±6.16		0.393*
Type of Delivery								0.897+
	Vaginal	18	41.86%	28	45.16%	42	41.58%	
	Cesarean	25	58.14%	34	54.84%	59	58.42%	
Indications for Cesarean Sections								0.230+
	Previous Cesarean	13	52.00%	19	55.88%	35	59.32%	
	Fetal Distress	3	12.00%	5	14.71%	12	20.34%	
	Progress failure	4	16.00%	4	11.76%	5	8.47%	
	Cephalopelvic disproportion	3	12.00%	0	0.00%	5	8.47%	
	Macrosomia	1	4.00%	4	11.76%	0	0.00%	
	Malpresantation	1	4.00%	2	5.88%	2	3.39%	
Gravida								0.185‡
	Mean (SD)	2.81±1.39		2.32±1.14		2.56±1.61		
	Median (IQR)	3 (2-4)		2 (2-3)		2 (1-3.25)		
Parity								0.918‡
	Mean (SD)	1.19±1.1		1.11±0.96		1.28±1.29		
	Median (IQR)	1 (0-2)		1 (0-2)		1 (0-2)		
Placenta Grade								0.0001+
	1	0	0.00%	0	0.00%	70	68.63%	
	2	0	0.00%	0	0.00%	32	31.37%	
	3	43	100.00%	62	100.00%	0	0.00%	
Test week		30.16±1.76		35.16±0.64		31.48±3.34		0.0001*
Fetal Weight (g)		3213.6±560.67		3405.48±404.58		3205.54±368.27		0.01*
Gestational age at delivery (weeks)		38.35±2.08		38.94±1.12		38.67±1.54		0.168*
BMI		26.12±5.01		27.48±4.51		25.84±4.67		0.09*
Calcium (mg/dl)		8.75±0.39		8.7±0.49		8.75±0.33		0.680*
Magnesium (mg/dl)		1.78±0.15		1.77±0.21		1.75±0.13		0.616*
25(OH)D (µg)		14.5±7.46		13.92±7.29		14.66±8.37		0.839*
Gender	Female	17	39.53%	29	46.77%	43	42.16%	0.741+
	Male	26	60.47%	33	53.23%	59	57.84%	
Preeclampsia	No	40	93.02%	57	91.94%	96	94.12%	0.863+
	Yes	3	6.98%	5	8.06%	6	5.88%	
LBW	No	38	88.37%	62	100.00%	97	95.10%	0.024+
	Yes	5	11.63%	0	0.00%	5	4.90%	
SGA	No	40	93.02%	62	100.00%	96	94.12%	0.128+
	Yes	3	6.98%	0	0.00%	6	5.88%	
Fetal demise	No	42	97.67%	62	100.00%	102	100.00%	0.147+
	Yes	1	2.33%	0	0.00%	0	0.00%	
GDM	No	40	93.02%	59	95.16%	95	93.14%	0.855+
	Yes	3	6.98%	3	4.84%	7	6.86%	
Oligohydramnios	No	40	93.02%	59	95.16%	100	98.04%	0.321+
	Yes	3	6.98%	3	4.84%	2	1.96%	
Polyhydramnios	No	42	97.67%	61	98.39%	102	100.00%	0.351+
	Yes	1	2.33%	1	1.61%	0	0.00%	
PROM	No	42	97.67%	61	98.39%	94	92.16%	0.136+
	Yes	1	2.33%	1	1.61%	8	7.84%	
PPROM	No	43	100.00%	61	98.39%	101	99.02%	0.708+
	Yes	0	0.00%	1	1.61%	1	0.98%	
Macrosomia	No	41	95.35%	56	90.32%	100	98.04%	0.082+
	Yes	2	4.65%	6	9.68%	2	1.96%	
Preterm birth	No	38	88.37%	59	95.16%	89	87.25%	0.250+
	Yes	5	11.63%	3	4.84%	13	12.75%	
Postterm birth	No	42	97.67%	62	100.00%	99	97.06%	0.406+
	Yes	1	2.33%	0	0.00%	3	2.94%	
Abruptio Placantae	No	41	95.35%	62	100.00%	101	99.02%	0.125+
	Yes	2	4.65%	0	0.00%	1	0.98%	

* One-way Analysis of Variance ,‡ Kruskal Wallis Test ,+Chi-Square test, Group 1, women with early preterm placental calcification (noted at 24-32 week's gestation); Group 2, women with late preterm placental calcification (noted at 32-36 week's gestation); Group 3 controls,i.e. women with no placental calcification noted on ultrasound at 24-36 week's gestation, BMI: Body mass index (kg/m2), LBW: Low birth weight, SGA: Small for gestational age, GDM: Gestational diabetes mellitus, PROM: Premature rupture of membrane, PPROM: Preterm premature rupture of membrane

DISCUSSION

Placental calcification (PC) is a common condition showing maturation and aging of the placenta and smoking low parity, and young age are the most important predisposing factors (9). When seen before the 36th gestational week, it is called preterm placental calcification (PPC) and PPC was determined as 3.8% at 36weeks and 23.7% between 31-34 gestational weeks (5). In our study, LBW was observed more frequently in the early PPC group than in the late PPC group. Oligohydramnios was more common in the early and late PPC patients compared to non-PPC pregnant women. However, oligohydramnios and LBW were not found statistically significant in logistic regression analysis. In addition, we observed no statistically significant difference regarding other adverse obstetric outcomes such as SGA, preeclampsia, fetal death, GDM, polyhydramnios, PROM, PPROM, macrosomia, preterm birth, postterm birth and abruptio placenta.

Some histological changes in placenta may be related to pregnancy complications (13-15). Goswami et al. (16) explained that PCC occurs as an inadequate uteroplacental blood flow, and one of the factors playing a role in insfficent uteroplacenta is excessive calcium accumulation in villus. Considering this mechanism, we investigated the relationship between calcium, magnesium and vitamin D and PPC in our study. In a study, the authors were not found any difference between the late preterm and term pregnancies for placental pathologies. (17). Yin et al. (18) examined placentas after birth and found that this grading in term placentas did not reflect the functional capacity of the placenta.

After synthesized in placenta, vitamin 24-25 (OH) D have a role in ossification in fetus and absorption of calcium from fetal intestines (19). We can also demonstrate that the deficiency of vitamin D is common among women. Certain hormones such as vitamin D, parathyroid hormone and calcitonin may play a role in PC (20,21). In some of the studies, calcium levels in fetus and pregnant women were found to be higher in patients with PC (9). Both deficiency of vitamin D and PC were found to be associated with intrauterine growth retardation (IUGR) (2), GDM (22) and pre-eclampsia (23). Hypovitaminosis D during pregnancy was found to be associated with preeclampsia and GDM, and it was stated that it could increase the risk of osteoporosis in the post-pregnancy life of the patient (24,25). Unlike other studies, we did not find any correlation between magnesium, calcium, vitamin D levels and PPC.

In the study of Vosmar et al. (22), it was stated that when PPC was seen, 60% SGA cases were born. However, while SGA was observed at a rate of 6.98% in our pregnant group with early PPC, SGA was not found in late PPC. In present study, with the comparision of 3 groups, there was no significant intergroup difference as for SGA.

There are also studies showing the relationship between abnormal Doppler ultrasonography imaging and IUGR with placental pathology (26,27). For evaluating the effects of placental mineral deposition, noninvasive imaging techniques are needed (28). Rossi et al. (29) proposed a new histopathological scoring system based on calcification pattern and grading, and evaluated IUGR with this scoring system.

In the study by Mc Kenna et al. (13) pregnant women with grade III placenta at 36th gestational week were examined and they found 3-fold increase in the risk of SGA and 5-fold increase in the risk of preeclampsia. In our study, preeclampsia was observed with a rate of 6.98% in the early PPC and 8.06% in the late PPC groups. In patients without PPC, preeclampsia rate was 5.88% and between the groups there was no significant difference.

When the relationship between PC and longterm cardiovascular health is examined, the calcification of coronary artery increases the risk 3.5 times when there was a history of preeclampsia. (14,30). In another study, pregnant women with grade III PC between 31th and 34th gestational weeks were examined and increases in incidence of IUGR (6.20%), fetal distress (7.8%), and LBW (34.37%) were observed (31).

In a study examining the relationship between LBW and the pathological changes of the placenta, deposition of subchorionic fibrin and calcification were seen in significantly higher numbers from LBW delivered patients than controls (32). However in another study, they found that the risk of oligohydramnios, and LBW increased in pregnants with PC at their <37 gestational weeks (33). In our study, oligohydramnios increased 3.75 times in the early PPC group and 2.54 times in the late PPC group compared to the non-PPC group. However, increase in the risk was not found significant in multivariate analysis.

In the study of Chen et al. (5) although hemorrhage, abruption of placenta and maternal intensive care unit admission (ICU), preterm birth and LBW were more common in early PPC group. But in the late PPC group adverse obstetric problems were not observed. In our study, we observed a statistically significant difference between LBW distributions (p=0.024). While no LBW was found in the late PPC group, LBW was found in the 11.63% of the pregnants in the early PPC group at <32 gestational weeks. When the early and late PPC groups were compared, the rate of LBW was higher in the early PPC. (p=0.022) However, any statistically significant difference was not detected in logistic regression analysis.

A relationship was found between excessive placental calcification and gestational hypertension, placental abruption and IUGR (34). When the authors were examined the liaison between intravillous and intrafibrinous microcalcification and obstetric problems, they found that the risk for intrauterine death increased. (35). In another study, when PPC occure at 28 weeks of gestation, there was a correlation with demise of fetus (36). In the meta-analysis, they found that placental calcification was seen with LBW, labor induction and death of the fetus (37). In our study, fetal demise was observed at a rate of 2.33% in the early PPC group, while no fetal demise was observed in the late PPC group and the group without PPC.

We acknowledge that this study has some limitations Data related to race, socioeconomic status, education and nutritional status of the mother were not analyzed. The results might be affected by these factors.

CONCLUSION

In conclusion, preterm placental calcifications might be seen with obstetric complications. However, in our study early and late PPC did not increase the risk for adverse outcomes such as preeclampsia, SGA, fetal demise, GDM, oligohydramnios, polyhydramnios, PROM, PPROM, macrosomia, preterm birth, postterm birth and abruptio placenta. Although LBW was observed significantly more frequently in the early PPC group; increase in the risk associated with PPC was not observed in multivariate analysis and there was also no significant difference in maternal calcium, magnesium and vitamin D levels between the study groups. We think that PPC alone is not effective in determining fetal prognosis. Our study differs from previous studies in that it is a prospective study with a large patient group, where we examined the relationship between maternal calcium, magnesium and vitamin D levels with PPC. However, large-scale studies, in which maternal and fetal prognosis can be examined after birth are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Okmeydanı Training and Research Hospital Ethics Committee (Date: 23/12/2019, Decision No: 48670771-514.10./1511).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Poggi SH, Bostrom KI, Demer LL, Skinner HC, Koos BJ. Placental calcification: a metastatic process? Placenta 2001; 22: 591-6.
2. Grannum PA, Berkowitz RL, Hobbins JC. The ultrasonic changes in the maturing placenta and their relation to fetal pulmonic maturity. Am J Obstet Gynecol 1979; 133: 915-22.
3. Mastrolia SA, Weintraub AY, Sciaky-Tamir Y, Tirosh D, Loverro G, Hershkovitz R. Placental calcifications: a clue for the identification of high-risk fetuses in the low-risk pregnant population? J Matern Fetal Neonatal Med 2016; 29: 921-7.
4. Miller JM Jr, Brown HL, Kissling GA, Gabert HA. The relationship of placental grade to fetal size and growth at term. Am J Perinatol 1988; 5: 19-21.
5. Chen KH, Chen LR, Lee YH. Exploring the relationship between preterm placental calcification and adverse maternal and fetal outcome. Ultrasound Obstet Gynecol 2011; 37: 328-34.
6. Jamal A, Moshfeghi M, Moshfeghi S, Mohammadi N, Zarean E, Jahangiri N. Is preterm placental calcification related to adverse maternal and foetal outcome? J Obstet Gynaecol 2017; 37: 605-9.
7. Lemancewicz A, Laudańska H, Laudański T, Karpiuk A, Batra S. Permeability of fetal membranes to calcium and magnesium: possible role in preterm labour. Hum Reprod 2000; 15: 2018-22.
8. Czajkowski K, Wójcicka-Bentyn J, Grymowicz M, Smolarczyk R, Malinowska-Polubiec A, Romejko E. Calcium-phosphorus-magnesium homeostasis in pregnant women after renal transplantation. Int J Gynaecol Obstet 2003; 80: 111-6.
9. Bedir Findik R, Ersoy AO, Fidanci V, Tasci Y, Helvacioglu Y, Karakaya J. Vitamin D deficiency and placental calcification in low-risk obstetric population: are they related? J Matern Fetal Neonatal Med 2016; 29: 3189-92.
10. Ergür AT, Berberoğlu M, Atasay B, et al. Vitamin D deficiency in Turkish mothers and their neonates and in women of reproductive age. J Clin Res Pediatr Endocrinol 2009; 1: 266-9.
11. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001; 20: ix-xiv.
12. Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol 2018; 131: e49-e64.
13. McKenna D, Tharmaratnam S, Mahsud S, Dornan J. Ultrasonic evidence of placental calcification at 36 weeks' gestation: maternal and fetal outcomes. Acta Obstet Gynecol Scand 2005; 84: 7-10.
14. Wallingford MC, Benson C, Chavkin NW, Chin MT, Frasch MG. Placental vascular calcification and cardiovascular health: ıt ıs time to determine how much of maternal and offspring health ıs written in stone. Front Physiol 2018; 9: 1044.
15. Guo Y, Zhang D, Lu H, Luo S, Shen X. Association between calcifying nanoparticles and placental calcification. Int J Nanomedicine 2012; 7: 1679-86.
16. Goswami P, Memon S and Pardeep K. Morphological, histological and radiological study of calcified placenta and its relation with foetal outcome. IOSR J Dental Med Sci 2013; 7: 82-8.
17. Ericksen K, Fogel J, Verma RP. Placental histopathology in late preterm infants: clinical implications. Clin Exp Pediatr 2020; 63: 48-51.

18. Yin TT, Loughna P, Ong SS, Padfield J, Mayhew TM. No correlation between ultrasound placental grading at 31-34 weeks of gestation and a surrogate estimate of organ function at term obtained by stereological analysis. Placenta 2009; 30: 726-30.
19. Kaushal M, Magon N. Vitamin D in pregnancy: a metabolic outlook. Indian J Endocrinol Metab 2013; 17: 76-82.
20. Mitchell DM, Jüppner H. Regulation of calcium homeostasis and bone metabolism in the fetus and neonate. Curr Opin Endocrinol Diabetes Obes 2010; 17: 25-30.
21. Ohata Y, Yamazaki M, Kawai M, et al. Elevated fibroblast growth factor 23 exerts its effects on placenta and regulates vitamin D metabolism in pregnancy of Hyp mice. J Bone Miner Res 2014; 29: 1627-38.
22. Vosmar MB, Jongsma HW, van Dongen PW. The value of ultrasonic placental grading: no correlation with intrauterine growth retardation or with maternal smoking. J Perinat Med 1989; 17: 137-43.
23. Liu NQ, Ouyang Y, Bulut Y, et al. Dietary vitamin D restriction in pregnant female mice is associated with maternal hypertension and altered placental and fetal development. Endocrinology 2013; 154: 2270-80.
24. Shin JS, Choi MY, Longtine MS, Nelson DM. Vitamin D effects on pregnancy and the placenta. Placenta 2010; 31: 1027-34.
25. Sofi NY, Jain M, Kapil U, et al. Status of Serum Vitamin D and Calcium Levels in Women of Reproductive Age in National Capital Territory of India. Indian J Endocrinol Metab 2017; 21: 731-3.
26. Barati M, Masihi S, Barahimi E, Khorrami MA. Relationship between placental calcification and estimated fetal weight percentile at 30-34 weeks of pregnancy. Int J Women's Health Reproduct Sci 2019; 7: 478-82.
27. Spinillo A, Gardella B, Bariselli S, Alfei A, Silini E, Dal Bello B. Placental histopathological correlates of umbilical artery Doppler velocimetry in pregnancies complicated by fetal growth restriction. Prenat Diagn 2012; 32: 1263-72.
28. Moran M, Higgins M, Zombori G, Ryan J, McAuliffe FM. Computerized assessment of placental calcification post-ultrasound: a novel software tool. Ultrasound Obstet Gynecol 2013; 41: 545-9.
29. Rossi C, Gerosa C, Pampaloni P, et al. Placental Calcification Score: a new semiquantitative method to assess pattern and grading of placental calcifications. J Pediatr Neonat Individual Med [Internet] 2019; 8: e080206.
30. White WM, Mielke MM, Araoz PA, et al. A history of preeclampsia is associated with a risk for coronary artery calcification 3 decades later. Am J Obstet Gynecol 2016; 214: 519.e1-519.e8.
31. Chitlange SM, Hazari KT, Joshi JV, Shah RK, Mehta AC. Ultrasonographically observed preterm grade III placenta and perinatal outcome. Int J Gynaecol Obstet 1990; 31: 325-8.
32. Nigam J, Misra V, Singh P, Singh P, Chauhan S, Thakur B. Histopathological study of placentae in low birth weight babies in India. Ann Med Health Sci Res 2014; 4: S79-83.
33. Zhang LY, Yu YH, Hu ML. Association between ultrasonographic signs of placental premature aging and pregnancy outcome. Di Yi Jun Yi Da Xue Xue Bao 2005; 25: 318-20.
34. Agababov RM, Abashina TN, Suzina NE, Vainshtein MB, Schwartsburd PM. Link between the early calcium deposition in placenta and nanobacterial-like infection. J Biosci 2007; 32: 1163-8.
35. Zeng J, Marcus A, Buhtoiarova T, Mittal K. Distribution and potential significance of intravillous and intrafibrinous particulate microcalcification. Placenta. 2017; 50: 94-8.
36. Chen KH, Seow KM, Chen LR. The role of preterm placental calcification on assessing risks of stillbirth. Placenta 2015; 36: 1039-44.
37. Mirza FG, Ghulmiyyah LM, Tamim H, Makki M, Jeha D, Nassar A. To ignore or not to ignore placental calcifications on prenatal ultrasound: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2018; 31: 797-804.

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fT3 index/TSH index ratio and free thyroid hormone index in the differential diagnosis of thyrotoxicosis

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ABSTRACT

Aim: Common causes of thyrotoxicosis are hyperthyroidism and destructive thyroiditis. Hyperthyroidism is a condition characterized by high serum thyroid hormone levels as a result of over-synthesis of thyroid hormones, the most common causes of which are Graves' disease (GD) and toxic nodular goiter (TNG). Subacute thyroiditis (SAT) causes thyrotoxicosis due to the circulating thyroid hormones of destructive thyroiditis. Differential diagnosis is important because GD, TNG and SAT treatment approaches are different. The aim of this study was to analyze whether it is possible to make a differential diagnosis for these conditions by examining free thyroid hormones, fT3/fT4 ratio, fT3 index/TSH index (fT3I/TSHI) ratio and Free Thyroid Hormone Index (FTHI).

Material and Method: This retrospective study included 150 patients who were diagnosed with GD, TNG and SAT. The fT3 index (fT3I) was calculated as the ratio between the fT3 value and the fT3 upper limit of normal value (fT3I=fT3/4 pg/ml). The fT4 index (fT4I) was calculated as the ratio between the fT4 value and the fT4 upper limit of normal value (fT4I=fT4/1.23 mg/dl). The TSH index (TSHI) was calculated as the ratio between TSH value and the TSH lower limit of normal limit (TSHI=TSH/0.38 mIU/L). The FTHI index was calculated using the formula of (fT3 level/fT3 upper limit of normal) / (fT4 level/fT4 upper limit of normal).

Results: The fT3, fT3/fT4 ratio and FTHI were found to be higher in hyperthyroid patients compared to subacute thyroiditis patients. fT4 and fT3I/TSHI levels were similar in hyperthyroid patients and SAT patients (p=0.49, p=0.11, respectively). The cut-off level of FTHI for hyperthyroidism was determined as 0.97 with sensitivity of 75% and specificity of 76.3% (AUC=0.833, p< 0.001). When hyperthyroidic patients were divided into two groups as GD and TNG, no significant difference was found in fT3/fT4 ratio (p:0.99). The fT3 (p<0.001) and fT4 (p<0.001) values were found to be higher, and TSH values were found to be lower (p=0.001) in GD. The fT3I/TSHI ratio was found to be higher in Graves' patients (p<0.001). The cut off level for Graves' disease was determined as sT3I/TSHI>324.58.

Conclusion: FTHI is useful in differentiating hyperthyroid conditions such as GD and TNG from SAT. FTHI is insufficient in the differential diagnosis of Graves disease and TNG. The fT3I/TSHI ratio is higher in Graves' disease than in TNG and SAT. The combination of FTHI and sT3I/TSHI methods can increase diagnostic accuracy.

Keywords: Hyperthyroidism, free T4, T3/T4 ratio, graves disease, toxic nodular guatr, subacute thyroiditis

INTRODUCTION

Thyrotoxicosis is a condition characterized by an excess of thyroid hormones in the serum (1). There are two main mechanisms for the formation of thyrotoxicosis. The first is the mechanism called hyperthyroidism, characterized by increased thyroid hormone synthesis and secretion from the thyroid gland. The second type of thyrotoxicosis occurs as a result of destructive thyroiditis without an increase in hormone synthesis from the thyroid gland. In destructive thyroiditis, synthesized thyroid hormones enter the circulation and cause symptoms. The main causes of hyperthyroidism are Graves' Disease (GD) and toxic nodular goiter (TNG) (2). Subacute thyroiditis (SAT) is one of the causes of destructive thyroiditis (3,4). Differential diagnosis is essential since the treatment and follow-up of GD, TNG and destructive thyroiditis differ (5).

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Even if thyroid nodules are seen in ultrasonographic evaluation, differential diagnosis of thyrotoxicosis is difficult without scintigraphy. However, scintigraphic methods are contraindicated in cases such as pregnancy and breastfeeding (6). In addition, scintigraphic methods are not always accessible due to both the high cost and lack of availability in every center. Occasionally, radioactive iodine uptake is found to be low in hyperthyroid patients due to iodine contamination before the scintigraphic procedure. Radioactive iodine uptake may be high in the healing phase of destructive thyroiditis (7). In such scintigraphic limitations, TSH receptor antibodies are helpful in distinguishing GD from other conditions. However, there may be false-negative and false-positive results (8,9).

A total T3/total T4 ratio of <20 ng/mcg in thyrotoxic patients is considered an indicator of destructive thyrotoxicosis (7). Instead of total form, free T3 (fT3) and free T4 (fT4) measurements are more widely used because they are less affected by thyroid hormone binding proteins and are more accessible. The fT3/fT4 ratio has been reported as a useful indicator in differentiating subacute thyroiditis from Graves' disease (10,11). However, due to the limited number of studies and the heterogeneity of the studies, a clear recommendation cannot be made (12–18). Therefore, the aim of this study was to evaluate fT3 and fT4 ratios and levels in patients with Graves' disease, toxic nodular goiter and subacute thyroiditis.

MATERIAL AND METHOD

The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 19.04.2021, Decision no:109/39). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

This retrospective study included thyrotoxicosis patients aged >18 years who presented at the endocrinology and metabolic diseases polyclinics of a tertiary hospital between 2018 and 2020. All persons included in the study signed the informed consent form. Patients with GD, TNG and SAT were included in the study. Patients with breastfeeding, pregnancy, kidney and hepatic failure, cancer or infection, and those using drugs that affect thyroid functions were excluded from the study. The diagnoses of Graves' disease, toxic nodular goiter, and subacute thyroiditis were made according to the criteria in **Table 1**. The patients were first evaluated in two groups; GD and TNG patients were evaluated as the hyperthyroidism group and SAT patients were evaluated as the destructive thyroiditis group. Then the GD, TNG and SAT patients were evaluated separately.

Laboratory Analysis

Beckman Coulter chemiluminescent immunoassay device was used to measure thyroid function tests (CA, USA). Reference ranges were defined as TSH: 0.38-5.33 mIU/L, fT4: 0.60-1.25 ng/dl, fT3: 2.28- 4 pg/ml. The fT3 index (fT3I) was calculated as the ratio between the fT3 value and the upper limit of fT3 normal value (fT3I=fT3/4 pg/ml). The fT4 index (fT4I) was calculated as the ratio between the fT4 value and the upper limit of fT4 normal value (fT4I=fT4/1.23 mg/dl). The TSH index (TSHI) was calculated as the ratio between TSH value and the lower limit of TSH normal limit (TSHI=TSH/0.38 mIU/L). The Free Thyroid hormone index (FTHI) was calculated as fT3I/fT4I ratio. fT3/fT4, fT3I/TSH and sT3I/TSHI were calculated by dividing the parameters by each other.

Statistical Analysis

Shapiro Wilk test was used to evaluate the parametric distribution. Non-parametric variables were expressed as median (range) values. In comparison of non-parametric multiple groups the Kruskal–Wallis test, and in comparison of non-parametric two groups Mann–Whitney U test were used. Tamhane tests were used in multiple group post hoc analyses. Categorical variables relationships were examined via Chi-Square test. For differential diagnosis, a cut-off value was determined using ROC curve. A value of $p<0.05$ was considered statistically significant.

Table 1. Criteria used in the diagnosis of Graves' Disease, Subacute thyroiditis and Toxic Nodular Goiter

Graves' Disease	Toxic Nodular Goiter	Subacute thyroiditis
1. Diffuse enlargement of the thyroid gland, presence of ophthalmyopathy/dermopathy 2. Increased/inappropriate normal fT3 and fT4, with suppressed TSH 3. Increased TSH receptor antibody level 4. Increased blood flow on ultrasonography 5. Diffuse hyperplasic thyroid gland on scintigraphy	1. Increased/inappropriate normal fT3 and fT4, with suppressed TSH 2. Nodular appearance on ultrasonography 3. Toxic adenoma appearance on scintigraphy	1. Painful, tender and hard thyroid gland 2. Elevated ESR, CRP 3. Increased/inappropriate normal fT3 and fT4, with suppressed TSH 4. Ultrasonographically indistinct, hypoechoic areas with decreased blood supply, painful when pressing the probe

RESULTS

The mean age of the participants was 50±15 years. When the patients were evaluated in two groups as the hyperthyroidic group and destructive thyroiditis, the patients with destructive thyroiditis were seen to be younger (p<0.001). The gender distribution of hyperthyroidic patients and patients with destructive thyroiditis was similar (p=1.00). The fT3, fT3I, fT3/fT4 ratio and FTHI were found to be higher in hyperthyroid patients (p=0.04, p=0.04, p<0.001 and p<0.001; respectively) (**Table 2**). The optimal cut-off value for FTHI was determined as 0.97 and for fT3/fT4, 3.12 (**Table 3**).

Table 2. Comparisons of the demographic and laboratory values of the hyperthyroidic group and subacute thyroiditis group

	Hyperthyroidism (GD+TNG) n:100	Destructive thyroiditis (SAT) n:50	p
Age (years)	52 (22-87)	40 (27-71)	**<0.001**
Gender (F(%)/M(%))	74 (74%)/26(26%)	37(74%)/13(26%)	1.00
fT3 (pg/ml)	5.17 (2.60-30.00)	4.48 (2.37-11.28)	**0.04**
fT4 (ng/dl)	1.69 (0.61-7.77)	1.71 (0.83-4.55)	0.57
TSH (mIU/L)	0.007 (0.001-0.67)	0.02 (0.003-0.9)	0.88
TSH Index	0.18 (0.001-1.76)	0.53 (0.01-2.37)	0.88
fT3 Index	1.29 (0.65-7.50)	1.12 (0.59-2.82)	**0.04**
fT4 Index	1.35 (0.49-6.22)	1.37 (0.66-3.64)	0.57
fT3/fT4	3.83 (2.11-10-99)	2.56 (1.45-4.24)	**<0.001**
FTHI	1.19 (0.66-3.43)	0.80 (0.45-1.33)	**<0.001**
fT3/TSH	1005 (5.33-23900)	233.75 (4.99-3760)	0.11
fT3I/TSHI	95.48 (0.51-2270.50)	22.20 (0.47-357.20)	0.11

GD: Graves Disease, TNG: toxic nodular goiter, SAT: subacute thyroiditis FTHI: free thyroid hormon index fT3I: fT3 index fT4I: fT4 index TSHI: TSH index

Table 3. Cut-off values for diagnosis of Hyperthyroidism according to ROC analysis

	Cut-off point	AUC	CI (95%)	Specificity (%)	Sensitivity (%)	p
FTHI	0.97	0.833	0.758-0.907	75	76.5	<0.001
fT3/fT4	3.12	0.833	0.758-0.907	76.3	75	<0.001
fT3	4.75	0.618	0.515-0.721	56.9	60.5	0.001

FTHI: Free Thyroid Hormone Index

Evaluation was made of 50 Graves patients, 50 toxic nodular goiter, and 50 subacute thyroiditis patients. The mean age of patients was 50.50 (30-75) years for GD, 60.50 (22-87) years for TNG, and 40 (27-71) years for SAT. No significant difference was found between the ages of GD and TNG patients (p=0.061). The age of SAT patients was found to be significantly younger than that of both GD and TNG patients (p<0.001 and p<0.001, respectively). No significant difference was found between the gender distribution of GD, TNG and SAT patients (p=0.19) (**Table 4**).

TSH levels of GD patients were 0.003 (0.001-0.35) mIU/L. TSH levels of GD patients were lower than TNG and SAT patients (p>0.001 and p=0.04, respectively). There was no difference between the TSH of the SAT and TNG groups (p=0.70).

There was no difference between the fT3 levels of SAT and TNG patients (p=0.95). The fT3 level of GD patients was higher than that of both TNG and SAT patients (p<0.001). The fT3I of GD patients was 2.34 (1.03-7.50). The fT3I value was higher in GD patients than in TNG and SAT patients (p<0.001). No difference was found between the fT3I values of TNG and SAT patients (p=0.95) (**Table 5**).

The fT4 level was 2.36 (0.87-7.77) ng/dl in patients with GD, 1.050 (0.61-4.00) ng/dl in TNG patients, and 1.71 (0.83-4.55) ng/dl in SAT patients. The fT4 levels of all three groups were significantly different from each other (p<0.001). The fT4I level was 0.84 (0.49-3.20) in GD patients, 1.37 (0.66-3.64) in SAT patients, and 0.84 (0.49-3.20) in TNG patients. The fT4I values of all three groups were significantly different from each other (p<0.001) (**Table 5**).

The fT3/fT4 ratio of SAT patients was 2.56 (1.45-4.24), which was significantly lower than that of GD and TNG patients (p<0.001). The fT3/fT4 ratio of the Graves disease and TNG groups did not differ (p=0.99). The FTHI value was lower in SAT patients than in GD and TNG patients (p<0.001). There was no difference in the FTHI values of GD and TNG patients (p=0.99) (**Table 5**).

Table 4. Comparisons of the demographic and laboratory values of patients with subacute thyroiditis, toxic nodular goiter and Graves' disease

	Graves Disease	Toxic Nodular Goiter	Subacute thyroiditis	p
Age (years)	50.50 (30-75)	60.50 (22-87)	40 (27-71)	<0.001
Gender (F(%)/M(%))	33(66%)/17(34%)	41(82%)/9(18%)	37(74%)/13(26%)	0.19
fT3 (pg/ml)	9.38 (4.14-30.00)	4.12 (2.60-20.00)	4.48 (2.37-11.28)	<0.001
fT4 (ng/dl)	2.36 (0.87-7.77)	1.050 (0.61-4.00)	1.71 (0.83-4.55)	<0.001
TSH (mIU/L)	0.003 (0.001-0.35)	0.04 (0.003-0.67)	0.02 (0.003-0.9)	<0.001
TSH Index (TSHI)	0.008 (0.00-0.92)	0.105(0.01-1.76)	0.53(0.01-2.37)	<0.001
fT3I	2.34 (1.03-7.50)	1.03 (0.65-5.00)	1.12 (0.59-2.82)	<0.001
fT4I	1.88 (0.70-6.22)	0.84 (0.49-3.20)	1.37 (0.66-3.64)	<0.001
fT3/fT4	3.72 (2.51-8.23)	3.95 (2.11-1.99)	2.56 (1.45-4.24)	<0.001
FTHI	1.16 (0.79-2.57)	1.23 (0.66-3.43)	0.80 (0.45-1.33)	<0.001
fT3/TSH	2118.33 (12.77-23900)	101.05 (5.33-2963.33)	233.75 (4.99-3760)	<0.001
fT3I/TSHI	201.24 (1.21-2270.50)	9.60 (0.51-281.52)	22.20 (0.47-357.20)	<0.001

FTHI: free thyroid hormon index fT3I: fT3 index fT4I: fT4 index TSHI: TSH index

Table 5. Post hoc analysis results of the demographic and laboratory values of patients with Graves' Disease, toxic nodular goiter and subacute thyroiditis.

	Graves Diasease	Toxic Nodular Goiter	p	Graves Diasease	Subacute thyroiditis	p	Toxic Nodular Goiter	Subacute thyroiditis	p
Age (years)	50.50 (30-75)	60.50 (22-87)	0.61	50.50 (30-75)	40 (27-71)	<0.001	60.50 (22-87)	40 (27-71)	<0.001
fT3 (pg/ml)	9.38 (4.14-30.00)	4.12 (2.60-20.00)	<0.001	9.38 (4.14-30.00)	4.48 (2.37-11.28)	<0.001	4.12 (2.60-20.00)	4.48 (2.37-11.28)	0.955
fT4 (ng/dl)	2.36 (0.87-7.77)	1.050 (0.61-4.00)	<0.001	2.36 (0.87-7.77)	1.71 (0.83-4.55)	0.003	1.050 (0.61-4.00)	1.71 (0.83-4.55)	<0.001
TSH (mIU/L)	0.003 (0.001-0.35)	0.04 (0.003-0.67)	0.001	0.003 (0.001-0.35)	0.02 (0.003-0.9)	0.04	0.04 (0.003-0.67)	0.02 (0.003-0.9)	0.705
TSH Index (TSHI)	0.008 (0.00-0.92)	0.105 (0.01-1.76)	0.001	0.008 (0.00-0.92)	0.53 (0.01-2.37)	0.04	0.105 (0.01-1.76)	0.53 (0.01-2.37)	0.705
sT3I	2.34 (1.03-7.50)	1.03 (0.65-5.00)	<0.001	2.34 (1.03-7.50)	1.12 (0.59-2.82)	<0.001	1.03 (0.65-5.00)	1.12 (0.59-2.82)	0.955
sT4I	1.88 (0.70-6.22)	0.84 (0.49-3.20)	<0.001	1.88 (0.70-6.22)	1.37 (0.66-3.64)	0.003	0.84 (0.49-3.20)	1.37 (0.66-3.64)	<0.001
fT3/fT4	3.72 (2.51-8.23)	3.95 (2.11-1.99)	0.99	3.72 (2.51-8.23)	2.56 (1.45-4.24)	<0.001	3.95 (2.11-1.99)	2.56 (1.45-4.24)	<0.001
FTHI	1.16 (0.79-2.57)	1.23 (0.66-3.43)	0.99	1.16 (0.79-2.57)	0.80 (0.45-1.33)	<0.001	1.23 (0.66-3.43)	0.80 (0.45-1.33)	<0.001
fT3/TSH	2118.33 (12.77-23900)	101.05 (5.33-2963.33)	<0.001	2118.33 (12.77-23900)	233.75 (4.99-3760)	0.001	101.05 (5.33-2963.33)	233.75 (4.99-3760)	0.476
fT3I/TSHI	201.24 (1.21-2270.50)	9.60 (0.51-281.52)	<0.001	201.24 (1.21-2270.50)	22.20 (0.47-357.20)	0.001	9.60 (0.51-281.52)	22.20 (0.47-357.20)	0.476

FTHI: free thyroid hormon index fT3I: fT3 index fT4I: fT4 index TSHI: TSH index

For GD-TNG differential diagnosis, the fT3I/TSHI ratio of 324.58 was determined as the cut-off point for Graves' disease with 77.8% sensitivity and 86.1% specificity (AUC: 0.882 , 95%CI: 0.804-0.961, p<0.001) (**Figure 1**).

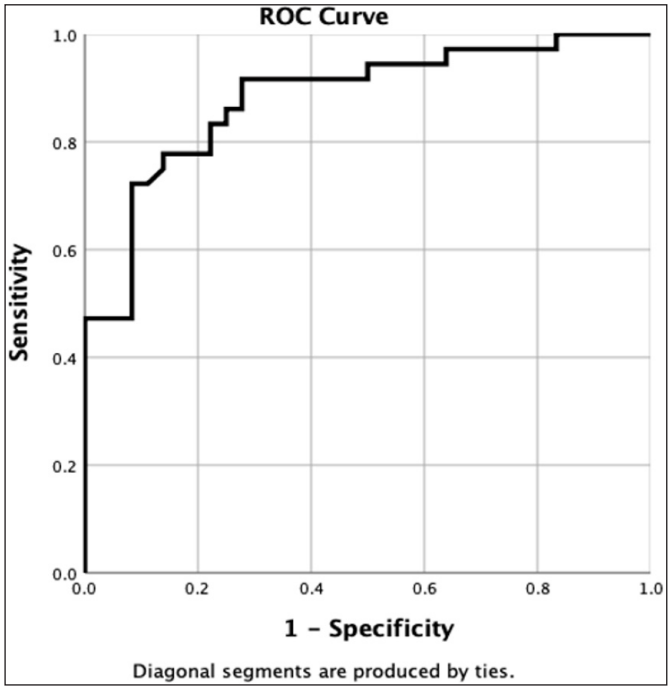

Figure 1. ROC curve analysis for FT3 index/TSH index

DISCUSSION

Ultrasonography, TSH receptor antibody level, and thyroid scintigraphy are the recommended methods in the differential diagnosis of Graves disease, TNG and SAT (19). In the current study, evaluations were made of the tests that can be applied for differential diagnosis in cases where these methods cannot be used. The results of the study demonstrated that FTHI and fT3/fT4 ratio can be used in the differential diagnosis of hyperthyroidism-destructive thyroiditis with 75% sensitivity and 76.5% specificity. It was observed that both fT3/fT4 ratio and FTHI were insufficient in distinguishing GD-TNG in hyperthyroid patients. From ROC analysis, it was determined that the fT3/TSH ratio has diagnostic value for GD-TNG differentiation. Thyrotoxicosis was seen to be more severe in GD patients.

Many studies have found the fT3/fT4 ratio to be useful in distinguishing between hyperthyroidism and destructive thyroiditis. Bahadır et al. (13) determined the optimal cut-off value for GD as 2.96 with sensitivity of 71.7% and specificity of 91.4%. Sriphrapradang (15) defined the fT3/fT4 cut-off value as 4.4 with 47.2% sensitivity and 92.8% specificity. There are also studies which have reported a cut-off value of 0.41, 0.86 and 2.8 for the fT3/fT4 ratio (10, 17, 20). The cut-off value of the fT3/fT4 ratio differs in all these studies, which can be attributed to the

different measurement units and reference range used. In addition, as in the study by Chen et al. (20), study design differences such as the participation of healthy control subjects in the ROC analysis change the results.

It can be considered that a differential diagnosis made using a method independent of measurement units, such as FTHI, will yield more objective results. In a study by Sumbul et al. (17), although a significant difference was found between hyperthyroid and destructive thyroiditis patients in terms of FTHI, ROC analysis was not performed. However, while the FTHI was >1 in all patients in the GD group, it was <1 in all patients in the thyroiditis group. Similarly in the current study, a cut-off value of 0.97 was determined for FTHI for the differential diagnosis of hyperthyroidism and subacute thyroiditis. However FTHI was insufficient in the differential diagnosis Graves' disease and TNG.

In a recent study by Wu et al. (16), the fT3/TSH ratio was found to be beneficial in the differential diagnosis of hyperthyroidism -thyrotoxicosis, although the hyperthyroidism group in that study only consisted of GD patients. In the current study, the fT3I/TSHI ratio was used because it is independent of the measurement method. The fT3I/TSHI ratio was found to be significantly higher in GD patients. The fT3/TSH ratio in Graves' patients was also found to be higher than in TNG patients. This is because thyrotoxicosis is more severe in Graves patients.

The FTHI cut-off point of >0.97 was found to be significant for hyperthyroidism and the fT3I/TSHI cut-off point of >324.58 was significant for GD. Therefore, in the case of FTHI>0.97 and fT3I/TSHI>324.58, the diagnosis of GD may be considered in the foreground. TNG can be considered if FTHI>0.97 and fT3I/TSHI<324.58. In case of FTHI<0.97 and fT3I/TSHI<324.58, SAT can be considered.

The main limitation of this study was that it was a single center, retrospective study. The small sample size was another limitation. In addition, iodine levels may change fT3 and fT4 levels. As it was a retrospective study, patients were not evaluated for iodine levels. Since this study was conducted in an iodine-deficient region, these results can be valid for iodine-deficient regions.

CONCLUSION

According our results, FTHI and fT3I/TSHI are useful criteria in the differential diagnosis of hyperthyroidism-thyrotoxicosis, with cut-off points of 0.97 and 324.58, respectively. The fact that they are independent of measurement units increases the universality of these methods. It may be appropriate to use FTHI and sT3I/TSHI methods together. Nevertheless, further studies are needed to confirm these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 19.04.2021, Decision no:109/39).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Sharma A, Stan MN. Thyrotoxicosis: diagnosis and management. Mayo Clin Proc 2019; 94: 1048-64.
2. Kravets I. Hyperthyroidism: diagnosis and treatment. Am Fam Physician 2016; 93: 363-70.
3. Sarkar SD. Benign thyroid disease: what is the role of nuclear medicine? Semin Nucl Med 2006; 36: 185-93.
4. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. New Engl J Med 2003; 348: 2646-55.
5. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet 2016; 388: 906-18.
6. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines Of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017; 27: 315-89.
7. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016; 26: 1343-421.
8. Sencar ME, Çalapkulu M, Sakiz D, et al. Frequency of thyroid antibodies at the diagnosis of subacute thyroiditis. Turkish J Endocrinol Metab 2020; 24: 144-8.
9. Barbesino G, Tomer Y. Clinical review: clinical utility of TSH receptor antibodies. J Clin Endocrinol Metab 2013; 98: 2247.
10. Yoshimura Noh J, Momotani N, Fukada S, Ito K, Miyauchi A, Amino N. Ratio of serum free triiodothyronine to free thyroxine in graves' hyperthyroidism and thyrotoxicosis caused by painless thyroiditis. Endocr J 2005; 52: 537-42.
11. Izumi Y, Hidaka Y, Tada H, et al. Simple and practical parameters for differentiation between destruction-induced thyrotoxicosis and Graves' thyrotoxicosis. Clin Endocrinol (Oxf) 2002; 57: 51-8.
12. Shıgemasa C, Abe K, Tanıguchı S-I, et al. Lower serum free thyroxine (T4) levels in painless thyroiditis compared with Graves' disease despite similar serum total T4 levels. J Clin Endocrinol Metab 1987; 65: 359-63.
13. Tura Bahadır Ç, Yılmaz M, Kılıçkan E. Free triiodothyronine to free thyroxine ratio in the differential diagnosis of thyrotoxicosis and hyperthyroidism: a retrospective study. Int J Clin Pract 2021; 75: E14003.

14. Narkar R, Mishra I, Baliarsinha A, Choudhury A. Rapid differential diagnosis of thyrotoxicosis using T3/T4 ratio, Ft3/Ft4 ratio and color doppler of thyroid gland. Indian J Endocrinol Metab 2021; 25: 193.
15. Sriphrapradang C, Bhasipol A. Differentiating Graves' disease from subacute thyroiditis using ratio of serum free triiodothyronine to free thyroxine. Ann Med Surg 2016; 10: 69-72.
16. Wu Z, Zhu Y, Zhang M, et al. Serum ratio of free triiodothyronine to thyroid-stimulating hormone: a novel index for distinguishing Graves' disease from autoimmune thyroiditis. Front Endocrinol (Lausanne) 2021; 11: 1-7.
17. Sümbül HE, Acıbucu F. Graves' disease and thyroiditis can be differentiated using only free thyroid hormone levels. Eur Res J 2019; 6: 314-8.
18. Yanagisawa T, Sato K, Kato Y, Shimizu S, Takano K. rapid differential diagnosis of Graves' disease and painless thyroiditis using total T3/T4 ratio, TSH, and total alkaline phosphatase activity. Endocr J 2005; 52: 29-36.
19. Gilbert J. Thyrotoxicosis – investigation and management. Clin Med (Northfield Il) 2017; 17: 274-7.
20. Chen X, Zhou Y, Zhou M, Yin Q, Wang S. Diagnostic values of free triiodothyronine and free thyroxine and the ratio of free triiodothyronine to free thyroxine in thyrotoxicosis. Int J Endocrinol 2018; 2018: 1-8.

Original Article

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Efficacy of tocilizumab in severe COVID-19: a retrospective study

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ABSTRACT

Aim: Coronavirus disease 2019 (COVID-19) is a pandemic with potential life-threatening outcomes. The current study aims to demonstrate the effect of tocilizumab in COVID-19 related cytokine storm.

Material and Method: This retrospective cross-sectional study evaluated the patients who received tocilizumab for COVID-19 related cytokine storm between March and August 2020. Demographic, clinical, and laboratory findings were recorded. Computerized tomography (CT) scans, which were performed before tocilizumab infusion were scored. The characteristics of the patients who survived versus those who did not survive were assessed.

Results: There was a total of 137 patients, 99 (72.3%) male and 38 (27.7%) female, with a median age of 62 years. Eighty-six (62.7%) patients had severe; 51 (37.2%) patients had critical disease course. The mortality rate was 24.1%. Higher mortality rates were present among patients older than 65 years, females, and with comorbid diseases (p=0.02, p=0.031, and p=0.01, respectively). The non-survived group had higher rates of mechanical ventilation (MV) support (85.2%) and admission to the intensive care unit (58.8%) (p<0.05). CT scores were higher in patients who did not survive compared with those who survived. Old age, critical disease, MV support, extended lung opacifications were associated with mortality according to multivariate logistic regression analysis (OR CI= 0.781, p=0.029, p=0.002, p=0.018, p=0.047, respectively).

Conclusion: We consider that due to the effect of tosilizumab in inhibiting the early stages of inflammation, it can be effective in the treatment of severe COVID-19 patients, especially under 65 years old, not requiring MV, and without extended pulmonary lesions.

Keywords: COVID-19, interleukin 6, tocilizumab, treatment

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INTRODUCTION

A 2019 novel coronavirus (2019-nCoV), also named the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV2), cause the Coronavirus disease 2019 (COVID-19), which was first appeared in Wuhan, China, in December 2019, has been spread rapidly all over the world and defined as a pandemic in March 2020. During COVID-19, a wide variety of symptoms may occur from mild to severe, including fever, cough, and dyspnea. However, the most important cause of mortality is respiratory failure due to severe acute pneumonia and acute respiratory distress syndrome (ARDS). Approximately 80% of COVID-19 patients may be asymptomatic or have a mild disease course. Fifteen percent of the patients who may need oxygen support have severe disease. The remaining 5% have critical COVID-19. Critical patients may require mechanical ventilation (MV) support due to ARDS (1). Being elderly, having comorbidities, and possessing impaired immunity are risk factors for higher susceptibility and higher mortality rates (2). COVID-19 has still been threatening human health all over the world regarding complications and death.

There is no effective prophylactic or post-exposure therapy that has been demonstrated in randomized controlled trials yet. Effects of lopinavir/ritonavir and remdesivir are not superior to those of standard care

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(3–5). Although favipiravir is the most widely used drug for COVID-19, the efficacy on severe and critical patients is limited (3,6). Data regarding the effectiveness of chloroquine/hydroxychloroquine are contradictory (3,7). For excessive pulmonary involvement, an approved treatment is necessary to prevent worsened outcomes.

Interleukin (IL)-6, tumor necrosis factor-alpha (TNF-a), and IL-12 are pro-inflammatory cytokines that may lead to cytokine storm in case of excessive production. Cytokine storm is responsible for COVID-19 associated acute respiratory failure that is more frequent in severe COVID-19. After the onset of cytokine storm, patients may progress to a rapid worsening that may lead to multiple organ dysfunction and death (8). Therefore, early diagnosis and treatment of cytokine storm are crucial for healing severe patients. Recent clinical experience has shown that IL-6 is one of the most important cytokines involved in the COVID-19 associated cytokine storm (1). Therefore, using the anti-human IL-6 receptor antibody tocilizumab has been a promising strategy for these patients.

However, the data regarding the efficacy of tocilizumab in COVID-19 is contradictory (2,9,10). There is still need to show the effect of tocilizumab in COVID-19 patients with severe lung involvement. This study aimed to evaluate the effectiveness of tocilizumab on the survival of COVID-19 patients with severe and critical diseases.

MATERIAL AND METHOD

The study was approved by University of Health Sciences Non-interventional Researches Ethics Committee (Date: 27.05.2020, Decision No: 2020-198). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design, Participants, and Data Collection

This retrospective cross-sectional study included the patients who received tocilizumab due to COVID-19 related cytokine storm, out of 2470 hospitalized COVID-19 patients at Gülhane Training and Research Hospital between March 2020 and August 2020.

All participants were diagnosed with COVID-19 according to the national COVID-19 Guideline case definition (11). The patients with a positive COVID-19 polymerase chain reaction (PCR) test, ≥18 years old, and who received tocilizumab for cytokine storm related COVID-19 included in the study. Patients who received other anti-cytokine therapies were excluded.

Clinical follow-up of the patients in the hospital was carried out under the coordination of chest medicine, infectious disease, internal medicine and intensive care unit physicians. In our center, rheumatology consultation is requested for patients who have been considered to be a candidate for tocilizumab treatment because of development of cytokine storm. Medical records have been used for obtaining demographic and clinical characteristics. IL-6, CRP, D-dimer, ESR, ferritin, liver enzymes, and complete blood count recorded from patients' files. The CT scans, within 72 hours before tocilizumab administration, were scored by a radiologist. Fleischner Society scoring system used to describe the lesions in CT scans (12). The presence and the spread of active infiltrations were recorded for each case. A semi-quantitative assessment method was applied to measure the degree of lung infiltration of COVID-19 in computed tomography (CT) (13). A total of five lobs in both lungs were evaluated. The extent of lesions in each lobe was estimated visually and scored. Scores were as follows; 0: none, 1: affecting less than 25% of the lobe, 2: affecting 26-50% of the lobe, 3: affecting 51-75% of the lobe, and 4: affecting more than 75% of the lobe. The total score between 0 and 20; was calculated by the sum of the scores of each lobe.

Definitions and treatment

The patients were classified as severe or critical COVID-19 according to the disease severity. The severe COVID-19 disease was defined as if the patient fulfills the following criteria of severe systemic inflammatory response and additionally respiratory rate >30/minute or oxygen saturation <93% on room air at rest. The critical COVID-19 disease was defined as fulfilling the criteria for the severe systemic inflammatory response in addition to at least one of the following: (1) respiratory failure requiring MV, (2) shock, and other organ failures, or a need for admission to the intensive care unit (ICU) (9,10).

Patients received the treatment agents in line with national COVID-19 treatment recommendations. The standard treatment included hydroxychloroquine (with/without azithromycin), favipiravir, and vitamin C alone or in combination. Low molecular weight heparin was administered to patients with high D-dimer levels. For patients with high procalcitonin levels or bacterial growth in the blood culture, parenteral antibiotic treatments were initiated. Corticosteroids, intravenous immunoglobulin, immune plasma, anakinra, and tocilizumab are treatment options for patients who were unresponsive to standard therapy. All patients received tocilizumab in an initial dose of 8 mg/kg. Whether the first dose was considered insufficient, according to national guidelines, a second dose within 24 hours was administered (11).

Statistical Analysis

All statistical analyses were performed using the IBM Statistical Package for Social Sciences, Statistics for Windows, Version 24.0 (IBM Corp.; Armonk, NY: USA, Released 2016). The normality assumption was assessed

by using the Kolmogorov-Smirnov test. The variables that do not have normal distribution were expressed as median (minimum-maximum) and interquartile range (IQR) (25th and 75th percentiles) and categorical variables were summarized as counts and percentages. The significance of the difference between the two groups was investigated by the Mann-Whitney U test for variables that were not normally distributed. Fisher's exact test and Chi-square test were used for categorical variables. Binary Logistic Regression (Nagelkerke R Square value was given) was used for logistic regression analysis. A p-value <0.05 was considered as statistically significant.

RESULTS

There were 137 patients (99 male and 38 female) with a median age of 62 years. The most common manifestations were cough (89.7%), fever (89.0%), shortness of breath (83.9%), weakness and fatigue (53.2%), myalgia (51.8%), nausea and vomiting (24.8%), headache (22.6%), diarrhea (16.0%), and loss of sense of taste and smell (11.6%). The median time between symptom onset and hospitalization was 5 (2-6.5) days, and the median duration between symptom onset and tocilizumab administration was 9 (6.5-12) days (**Table 1**). The comorbid diseases existed in 91 (66.4%) patients. Eighty-six (62.7%) patients had severe, 51 (37.2%) patients had critical disease (**Table 1**). Sixty-eight (49.6%) patients received hydroxychloroquine, and 135 (98.5%) received favipiravir as an antiviral treatment. The other treatments used for the patients were shown in Table 1. None of the patients received additional anti-cytokine treatments after tocilizumab treatment. The median dose of tocilizumab was 600 (ranges between 560-600) mg. Only three patients received a second dose of tocilizumab as 400mg within 24 hours due to continuing clinical symptoms.

CRP, ESR, fibrinogen, leucocyte, and LDH levels decreased within 24-72 hours after tocilizumab administration (**Table 2**). The median level of IL-6 on the tocilizumab administration day was 98 (ranges between 64.6-145.8). The median level of IL-6 after tocilizumab elevated to 417.6 (ranges between 190.6-1034.7) (**Table 2**).

Thirty-three (24.1%) patients died and were categorized as the non-survived group. The mortality rate was increasing with aging (p=0.001). The mortality rates were higher among patients who were older than 65 years, females, and patients with comorbidity (p=0.02, p=0.031, and p=0.01, respectively) (**Table 3**). The most common comorbidities were diabetes mellitus in 41 (30.0%) patients and hypertension in 37 (27.0%) patients. Twenty-four (17.5%) patients had chronic heart disease, 13 (9.5%) patients had chronic renal failure, 9 (6.6%) patients had chronic obstructive pulmonary disease, 8 (5.8%) patients had bronchial asthma, and 6 (4.4%) patients had

Table 1. Demographical and clinical characteristics of the study group

Characteristics	Patients (n=137)
Age, years, median (Q1-Q3)	62 (49.5-72)
Gender, n (%)	
Female	38 (27.7)
Male	99 (72.3)
Time between symptom onset and hospitalization, day, median (Q1-Q3)	5 (2-6.5)
Time between symptom onset and TCZ infusion, day, median (Q1-Q3)	9 (6.5-12)
Time from first symptom to TCZ infusion, n (%)	
≤6 days	34 (24.8)
7-12 days	73 (53.3)
≥13 days	30 (21.9)
Disease severity, n (%)	
Severe	86 (62.8)
Critical	51 (37.2)
Respiratory rate before TCZ infusion, n (%)	
≤20	19 (13.9)
21-30	94 (68.6)
≥31	24 (17.5)
SaO2 < 93% on TCZ day, n (%)	136 (99.3)
Precense of Comorbidity, n (%)	91 (66.4)
Concomitant treatment, n (%)	
Favipiravir	135 (98.5)
LMWH	128 (93.4)
Parenteral antibiotics	107 (78.1)
Hydroxychloroquine	68 (49.6)
Azithromycin	31 (22.6)
Corticosteroid	16 (11.7)
IVIG	3 (2.2)
TCZ dose, mg, median (Q1-Q3)	600 (560-600)
Second TCZ administration, n (%)	3 (2.2)

TCZ: Tocilizumab, IVIG: Intravenous Immunoglobulin; LMWH: Low-molecular-weight heparin

Table 2. Laboratory findings of COVID-19 patients on TCZ treatment day and after TCZ

	TCZ day	24-72 hours after TCZ
CRP, mg/dL	169.0 (118-237.8)	64.1 (23.7-117.7)
IL-6, pg/mL	98 (64.6-145.8)	417.6 (190.6-1034.7)
ESR, mm/h	76 (59.5-86)	60 (36-76.2)
Fibrinogen,mg/dl	638 (496-769)	474 (400-636)
Ferritin, ng/mL	563.6 (342.0-989.2)	587.2 (305.1-926.5)
D-dimer, mg/L	1.24 (0.6-1.9)	1.3 (0.8-3.0)
WBC, $x10^3/\mu L$	7100 (5400-9450)	5400 (3900-8001)
Hgb, g/dL	13 (11.8-13.8)	13 (11.6-14.0)
Lymphocyte, $x10^3/\mu L$	800 (600-1000)	800 (550-1200)
Platelet, $x10^3/\mu L$	234 (189.5- 299.5)	312 (227.5-397)
AST, IU/L	40 (30.5-65)	55 (33-81.5)
ALT, IU/L	30 (19.5-46)	49 (26-90)
LDH, IU/L	430 (326-577)	415 (25.5-555.5)

Variables were given as median (Q1-Q3). TCZ: Tocilizumab, CRP: C reactive protein, IL: Interleukin, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, Hgb: Hemoglobin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

congestive heart failure. The prevalences of hypertension, congestive health failure, and chronic renal failure were higher in the non-survived group than the survived group (p=0.000, p=0.003, and p=0.003, respectively) (Table 3). In the non-survived group, the rates of the patients on MV support (85.2%) and those with admission in the ICU (58.8%) were higher than the survived group (p<0.05) (Table 3). There was no statistically significant difference between survived and non-survived patients in terms of antiviral, anticoagulant, antibiotics, and the other treatment options used before tocilizumab. Statistically significant differences in CRP, IL-6, ESR, fibrinogen, d-dimer, leucocyte, LDH and lymphocyte levels were found between survived and non survived groups (p=0.016, p=0.000, p=0.031, p=0.016, p=0.000, p=0.000, p=0.000; p=0.049, respectively) (**Table 3**).

CT scans determined ground glass opacity in 135 (98.5%) patients, consolidation in 105 (76.6%) patients, ARDS in 104 (75.9%) patients, pleural effusion in 17 (12.4%) patients, interstitial lung disease in 7 (5.1%) patients. According to 78 CT scans performed within 72 hours before tocilizumab treatment, total CT scores were higher in the non-survived group than the survived group (p=0.01). The rate of patients with CT scores equal to and above 10 was higher in the non-survived group (p=0.019) (Table 3). There was no statistically significant difference between the survived and the non-survived group in terms of the presence of consolidation, pleural effusion, ground-glass opacity, interstitial lung disease, and acute respiratory distress syndrome in CT scans (p>0.05).

In multivariate logistic regression analysis, mortality showed a positive correlation with aging, disease severity, being under MV support and having extent lung opacifications (OR CI, p=0.029, p=0.002, p=0.018, p=0.047, respectively) (**Table 4**).

Table 3. Clinical characteristics of the survived and non-survived groups

Characteristics	Survived (n= 104)	Non-survived (n= 33)	p-value
Age, years, median (Q1-Q3)	58.5 (48.5-68.5)	70 (63-75)	0.001***
Age≥ 65, n (%)	40 (63.5)	23 (36.5)	0.020*
Gender, n (%)			0.031*
Female	24 (63.2)	14 (36.8)	
Male	80 (80.8)	19 (19.2)	
Precense of comorbidity, n (%)	63 (69.2)	28 (30.8)	0.010*
Hypertension, n (%)	19 (51.4)	18 (48.6)	0.000*
Congestive heart failure, n (%)	1 (16.7)	5 (83.3)	0.003**
Chronic kidney disease, n (%)	5 (38.5)	8 (61.5)	0.003**
Disease severity, n (%)			0.000*
Severe	83 (96.5)	3 (3.5)	
Critical	21 (41.2)	30 (58.8)	
MV requirement before TCZ, n (%)	4 (14.8)	23 (85.2)	0.000*
ICU admission before TCZ, n (%)	21 (41.2)	30 (58.8)	0.000*
C reactive protein, mg/dL, median (Q1-Q3)	163.7 (113.4-226.1)	210.9 (149.7-267.0)	0.016***
Interleukin-6, pg/mL, median (Q1-Q3)	83.5 (58.2-134.0)	150.7 (96.9-259.6)	0.000***
Erythrocyte sedimentation rate, mm/h, median (Q1-Q3)	70 (57-85)	83 (70-88)	0.031***
Fibrinogen, mg/dl, median (Q1-Q3)	623 (490.5-707)	726 (550-900)	0.016***
D-dimer, mg/L, median (Q1-Q3)	1.1 (0.6-1.7)	1.9 (1.2-2.5)	0.000***
White blood cell, x103/µL, median (Q1-Q3)	6800 (5100-8350)	9700 (7500-11800)	0.000***
Lymphocyte, x103/µL, median (Q1-Q3)	800 (600-1050)	700 (400-900)	0.049***
Lactate dehydrogenase, IU/L, median (Q1-Q3)	415.5 (322.5-509.5)	580 (416-672)	0.000***
Total CT Score (within 72 hours before TCZ infusion day), (n=78), median (Q1-Q3)	8 (6-12)	13 (8-16)	0.010*
Total CT Score (within 72 hours before TCZ infusion day), n (%) (n=78)			0.019*
<10	38 (60.3)	4 (26.7)	
≥10	25 (39.7)	11 (73.3)	

TCZ: Tocilizumab, MV: Mechanical ventilation, ICU: Intensive care unit, CT: Computerized tomography,*Pearson Chi-Square, **Fisher's Exact Test, ***Mann Whitney U Test

Table 4. Multivariate logistic regression analysis of the non-survived patients

	Unstandardized Coefficients		95% Confidence Interval for B		Standardized Coefficients	p-value
	B	Std.Error	Lower	Upper	Beta	
Gender	1.195	.928	.535	20.371	3.303	.198
Age	-2.522	1.156	.008	.774	.080	.029*
Comorbidity	-.973	.993	.054	2.648	.378	.327
HT	-.974	.910	.063	2.248	.377	.285
CHF	-4.345	2.949	.000	4.197	.013	.141
Disease severity	-3.171	1.032	.006	.317	.042	.002*
MV support	-3.969	1.677	.001	.505	.019	.018*
CT Score	-1.717	.866	.033	.981	.180	.047*

R2= 0.781(Nagelkerke), HT: Hypertension, CHF: Congestive Heart Failure, MV: Mechanical ventilation, CT: Computerized tomography, * p < 0.05

DISCUSSION

Cytokine storm syndrome mediated by the uncontrolled secretion of proinflammatory cytokines has been observed in most of the severe and critical COVID-19 patients. Cytokine storm may cause multiorgan failure, respiratory failure, and at last mortality. At this stage, stopping the cytokine storm before leading to life-threatening entities is one of the main aims of the treatment. In this situation, the object of the treatment should be either decreasing the proinflammatory cytokine release or affecting receptors of the released cytokines at the target organs. Recently, one of the most favored treatment options is the drug targeting IL-6. The current study found that tocilizumab decreases mortality in patients who have not been admitted to ICU, not under MV support, in the early stages of the disease without extensive lung lesions in pulmonary CT and younger than 65 years old.

Cytokine syndrome may occur during inflammatory, infectious, and iatrogenic causes. It may proceed with fever, hyperferritinemia, multiple organ failure, and mortality as a result of overwhelming systemic inflammation (8). During COVID-19, similar to the other diseases which promote cytokine storm, IL-6 plays a crucial role in the progress of the disease to cytokine storm (2,14–16). High levels of IL-6 inhibit perforin/granzyme-mediated apoptosis by preventing the cytotoxic T lymphocytes and natural killer cells. As a result, an increased antigenic presentation from virally infected target cells may bring about an accelerated cytokine release. Also, viral replication provokes IFN mediated toll-like receptor activation that may then stimulate cytotoxic T lymphocytes and macrophages to release cytokines while inhibiting cytolytic functions (17–19). Physiologically, due to not expressing the IL-6 receptor, most of the cells do not respond to IL-6. However, the amplification of IL-6 during the cytokine storm widely activates the signaling pathways. IL-6 uses transmembrane and soluble receptors and binds to gp130 to realize intracellular signal transduction and gene expression (14). Tocilizumab can inhibit cytokine releasing syndrome in various steps by binding transmembrane and soluble receptors of IL-6. Treatment with tocilizumab seems to be a promising option for patients with cytokine storm syndrome (20).

In the current study, the rate of mortality was 24.1% among patients receiving tocilizumab. There was an association between mortality and being elderly, needing MV support, having critical COVID-19, and an extensive pulmonary parenchymal disease. Recent studies in the literature presented a more severe disease course and higher rates of mortality in older and immunosuppressive patients (2,21). Also, being elderly has been found as an independent risk factor for mortality for the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) infections (22,23). Aging may impair normal functions of T and B lymphocytes and increase the response of type 2 cytokines (IL-4, IL-6, IL-10, and IL-15) that may cause prolonged inflammation related to uncontrolled viral replication (24). Besides older patients own a higher rate of comorbidities and use multiple drugs, they may have exaggerated clinical findings of the cytokine storm syndrome and increased viral load. In the current study, the number of comorbidities was increasing with aging. Patients with hypertension, chronic heart failure, and moderate-severe chronic renal failure had more severe disease courses and higher mortality rates, similar to the studies in the literature (25,26). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers may extend SARS-CoV-2 viremia by increasing ACE2 protein secretion from epithelial cells due to ACE2 is a receptor of SARS-CoV-2. Concerning this, it is thought that patients with hypertension and who were using ACE inhibitors and angiotensin receptor blockers may have a more severe disease course and higher mortality rates (27). Additionally, a more intensified ACE2 protein secretion from alveolar epithelium in males may explain the more extensive and more severe disease course among male individuals (28). In the current study, the rate of male patients was statistically significantly higher, similar to the literature. Whereas, in the current study, the rate of mortality among female patients was higher than male patients.

To our knowledge of influenza and other viral respiratory infections, the mortality rates related to coronary artery disease may rise during the viremia (29). Also, new or worsening heart failure, arrhythmia, and myocardial infarction may occur (30). The present study found a higher mortality rate among patients with heart failure, also, an increased rate of comorbid coronary heart disease among all patients, similar to the study performed by Zhou et al. (30). Increased proinflammatory and procoagulant factors may prompt plaque rupture, ischemia, and thrombosis. Besides, secretion of ACE2 as a receptor of SARS-CoV-2 on cardiac myocytes and vascular endothelial cells may be a triggering factor for cardiac diseases (31).

In the current study, IL-6, CRP, ESR, LDH, fibrinogen, and D-dimer levels were statistically significantly higher in non-survived patients than the patients who survived on the day before tocilizumab administration. The lymphocyte count was significantly lower in the non-survived group than the survived group. Keske et al. (9) reported that after the onset of the cytokine storm, a progression in pulmonary involvement, a rapid decrease of oxygen levels, and a need for ICU admission may occur

within hours and days. Also, they found a relationship between mortality and high levels of CRP, ferritin, IL-6, and D-dimer in patients who were following up in ICU. Similarly, Xiaoling et al. (2) recommended the early administration of tocilizumab in patients with persistent fever, worsening clinical findings, and increasing IL-6 levels. Raising procoagulant factors, especially D-dimer levels higher than 1 μg/mL, was found to be associated with increased mortality (30). The elevation of acute phase reactants can be used as a sign of disease progression, also can be a sign of clinical deterioration. In consideration of the increased mortality risk of critical patients, before the critical stage of the disease tocilizumab should be administered to break the cytokine cycle. The current study also found critical patients who needed MV support had higher rates of mortality. When the time of tocilizumab administration is delayed, a lower survival rate may be observed among patients due to the increased need for MV support and a more severe disease course (32). Invasive MV support, immunosuppression, and extended lung lesions may increase the risk for secondary bacterial infections (10). Especially, in critical patients, instead of early MV, high flow oxygen support with a nasal cannula should be preferred.

The patients in the current study presented various stages and patterns of pulmonary parenchymal disease. Cough, fever, and dyspnea were the most prevalent symptoms determined. A recent study which compared clinical symptoms between the patients with and without pneumonia related to COVID-19 reported that the most frequent symptoms were cough, fever, and dyspnea, similar to our study (33). Wang et al. (26) reported that lung lesions, which were defined according to Fleischner Society, reach a peak between six to eleven days from the symptom onset and were seen as 83%-85% ground-glass opacity and consolidation. To evaluate the effect of lung lesions on mortality, CT performed at least six days after onset of the symptoms or within three days before tocilizumab was administered similarly to the study presented by Wang et al. (26). Stone et al. (34) performed a placebo-controlled randomized trial that showed tocilizumab had no benefit on having MV require and death. But, they did not compare the CT findings between the study groups. An association between mortality and the extent of lung opacifications was found in the current study, similar to the previous studies in the literature (35–37). In the current study, the mortality risk was being increased in patients with CT scores above 10. It was determined that for patients who thought to be in cytokine storm due to viremia, to influence survival rates, tocilizumab should be administered in early stages without diffuse pulmonary lesions on CT. In this context, 78.1% of patients received tocilizumab in the first 12 days after the symptom onset.

The crucial part of the treatment of COVID-19 related pneumonia is to prevent the mortality related to ARDS and multiorgan failure caused by the cytokine storm. General supportive treatments, oxygen support, anti-viral drugs (favipiravir, lopinavir, ritonavir, remdesivir, hydroxychloroquine), corticosteroids, anti-cytokine therapies (IL-1 and IL-6 inhibitors, ruxolitinib), intravenous immunoglobulin, and immune plasma can be used primarily (5,38,39). Tocilizumab was applied once in a maximum dose based on Chinese guidelines and a study performed by Keske et al (9). In a study performed to investigate the effectiveness of tocilizumab in the treatment of the cytokine releasing syndrome in cancer patients, it was stated that repetitive doses in certain intervals in line with the pharmacokinetic data is important for providing rapid acceleration of tocilizumab plasma levels and reaching appropriate plasma levels (40). Although there are no randomized controlled studies, the current data in the literature supports a dose of 400 mg (or 8 mg/kg) tocilizumab once can be sufficient for COVID-19 related pneumonia for decreasing mortality rate and preventing potential adverse events (2,9). The appropriate approach for tocilizumab treatment is adjusting the dose and repetition of the drug according to the severity of the disease, laboratory assessment, extent of pulmonary lesions, comorbidities, and additional treatments.

The current study has some limitations. A larger number of patients could have been included in a study on a pandemic virus. A control group containing non-severe patients or severe/critical patients who did not receive tocilizumab may be included. Further studies with prospective design may contribute by evaluating the clinical, laboratory, and radiologic values after tocilizumab treatment. No CT evaluation before tocilizumab day can be done in the patients under MV support or in ICU. Prospective studies performed with larger samples and had CT evaluation on the day of tocilizumab administration may give a worthwhile opinion to form specific cut-off values in scoring systems of CT evaluation and to choose the perfect time in terms of tocilizumab treatment.

CONCLUSION

In conclusion, the current study investigated the effect of tocilizumab treatment in COVID-19 and concomitant cytokine storm. Tocilizumab is effective on suppressing inflammation in the early phases, particularly among patients who are younger than 65 years old, have no need for MV, and have less parenchymal lung involvement. Mainly, in severe patients, considering increased levels of acute phase reactants and coagulation parameters, and deepened cytopenias may help for choosing the appropriate time for tocilizumab treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences Non-interventional Researches Ethics Committee (Date: 27.05.2020, Decision No: 2020-198).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020; 34: 101623.
2. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci 2020; 117: 10970-5.
3. Lu C-C, Chen M-Y, Lee W-S, Lee Y, Chang L. Potential therapeutic agents against COVID-19: What we know so far. J Chinese Med Assoc 2020; 83: 534-6.
4. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med 2020; 382: 2327-36.
5. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020; 382: 1787-99.
6. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering 2020; 6: 1192-8.
7. Million M, Lagier J-C, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis 2020; 35: 101738.
8. Behrens EM, Koretzky GA. Review: cytokine storm syndrome: looking toward the precision medicine era. Arthritis Rheumatol 2017; 69: 1135-43.
9. Keske Ş, Tekin S, Sait B, et al. Appropriate use of tocilizumab in COVID-19 infection. Int J Infect Dis 2020; 99: 338-43.
10. Morena V, Milazzo L, Oreni L, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. Eur J Intern Med 2020; 76: 36-42.
11. Republic of Turkey Ministry of Health COVID-19 (SARS CoV-2 Infection) Guideline. http://covid19.saglik.gov.tr/TR-66341/antisitokin-antiinflamatuar-tedaviler-koagulopati-yonetimi. Accessed November 2020.
12. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: Glossary of Terms for Thoracic Imaging. Radiology 2008; 246: 697-722.
13. Ooi GC, Khong PL, Müller NL, et al. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. Radiology 2004; 230: 836-44.
14. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol 2015; 16: 448-57.
15. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020; 92: 814-8.
16. Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol 2020; 38: 529-38.
17. Cifaldi L, Prencipe G, Caiello I, et al. Inhibition of natural killer cell cytotoxicity by interleukin-6: Implications for the pathogenesis of macrophage activation syndrome. Arthritis Rheumatol 2015; 67: 3037-46.
18. Lykens JE, Terrell CE, Zoller EE, Risma K, Jordan MB. Perforin is a critical physiologic regulator of T-cell activation. Blood. 2011; 118: 618–26.
19. Ruscitti P, Berardicurti O, Iagnocco A, Giacomelli R. Cytokine storm syndrome in severe COVID-19. Autoimmun Rev 2020; 19: 102562.
20. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. Autoimmun Rev 2020; 19: 102568.
21. Hu B, Zeng LP, Yang X Lou, et al. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathog 2017; 13: e1006698.
22. Hong KH, Choi JP, Hong SH, et al. Predictors of mortality in Middle East respiratory syndrome (MERS). Thorax 2018; 73: 286-9.
23. Choi KW, Chau TN, Tsang O, et al. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. Ann Intern Med 2003; 139: 715-23.
24. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis 2005; 41: S504-12.
25. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020; 8: e21.
26. Wang Y, Dong C, Hu Y, et al. Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. Radiology 2020; 296: E55-64.
27. Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect 2020; 53: 425-35.
28. Gwathmey TM, Shaltout HA, Nixon PA, et al. Gender differences in urinary ACE and ACE2 activities in adolescents. FASEB J 2008; 22: 940-6.
29. Blackburn R, Zhao H, Pebody R, Hayward A, Warren-Gash C. Laboratory-confirmed respiratory infections as predictors of hospital admission for myocardial infarction and stroke: Time-series analysis of English data for 2004-2015. Clin Infect Dis 2018; 67: 8-17.
30. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-62.
31. Gallagher PE, Ferrario CM, Tallant EA. Regulation of ACE2 in cardiac myocytes and fibroblasts. Am J Physiol Heart Circ Physiol 2008; 295: H2373-9.
32. Price CC, Altice FL, Shyr Y, et al. Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus disease 2019. Chest 2020; 158: 1397–408.
33. Li K, Wu J, Wu F, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol 2020; 55: 327-31.
34. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med 2020; 383: 2333-44.
35. Yuan M, Yin W, Tao Z, Tan W, Hu Y. Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China. PLoS One 2020; 15: e0230548.

36. Antonio GE, Wong KT, Tsui ELH, et al. Chest radiograph scores as potential prognostic indicators in severe acute respiratory syndrome (SARS). Am J Roentgenol 2005; 184: 734-41.
37. Li K, Chen D, Chen S, et al. Predictors of fatality including radiographic findings in adults with COVID-19. Respir Res 2020; 21: 146.
38. Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19 - A systematic review of current evidence. Ecancermedicalscience 2020; 14: 1022.
39. Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: the reality and challenges. J Microbiol Immunol Infect 2020; 53: 436-43.
40. Le RQ, Li L, Yuan W, et al. FDA Approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. Oncologist 2018; 23: 943-7.

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Our convalescent plasma experiences in COVID-19 patients hospitalized in the intensive care unit

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ABSTRACT

Objective: Despite vaccine and drug studies, convalescent plasma (CP) therapy remains an alternative treatment for coronavirus disease 2019 (COVID-19). In this study, we aimed to reveal the efficacy of CP therapy on mortality and the factors affecting it for the patients diagnosed with COVID-19 and acute respiratory distress syndrome (ARDS) which were followed in our intensive care unit (ICU).

Material and Method: The data (demographic characteristics, the amount of CP used, PaO_2/FiO_2, leukocyte, neutrophil, lymphocyte, D-Dimer, C-reactive protein (CRP), procalcitonin, ferritin values, and the clinical findings) of the patients who were hospitalized in the ICU with the diagnosis of COVID-19 and received CP treatment between 20 March and 20 October 2020 were analyzed retrospectively. Data of deceased patients (n=29) and survivors (n=50) were compared with each other and logistic regression analysis was performed to investigate the relationship with mortality.

Results: 79 patients who received 166 units of CP therapy after a mean of 13.45±3.6 days symptom onset, were identified. 96.2% of the patients had at least one concomitant disease. Mortality was observed in 29 (36.7%) of the patients. Mortality (5.1%) was less common in those receiving CP therapy within the first 14 days after the onset of symptoms. Patient age (p=0.041), neutrophil/lymphocyte ratio (p=0.004), CRP values (p=0.002), the number of comorbidities (p<0.001), PaO_2/FiO_2 ratio before CP (p=0.005), and the period when CP was first infused from symptom onset (p<0.001) had a statistically significant effect on mortality.

Conclusion: CP can be safely used to treat COVID-19. However, its positive effect is less observed in patients with the advanced stage of the disease, progressive deterioration of oxygenation, and a high number of comorbidities. For this reason, starting CP treatment at an early stage may increase its effectiveness.

Keywords: Convalescent (immune) plasma, COVID-19, intensive care unit, SARS-Cov-2

INTRODUCTION

As of December 2019, coronavirus disease 2019 (COVID-19) has spread all around the world, affecting millions of people and drawing attention to its high mortality. In this context, passive immunization practices, which have historical importance, have come to the fore again. Immune plasma therapy is a treatment method based on the transfusion of plasma obtained from donors who have recovered from COVID-19 disease and have no viral load. The terms "convalescent plasma (CP)" or "hyperimmune plasma" can also be used instead of immune plasma.

Immune plasma therapy has also been used in previous outbreaks of influenza virus A (H1N1), Ebola virus, SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus), and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) (1-3). The first randomized study on the use of convalescent plasma in COVID-19 patients was conducted in China (4). The study reported that there was no difference between mortality and hospital discharge rates at the end of 28 days, but a significant decrease in viral load occurred within 72 hours in the group treated with convalescent plasma.

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The US Food and Drug Administration (FDA) had approved the use of convalescent plasma therapy in patients with severe or life-threatening COVID-19 during the initial period of the pandemic but subsequently limited CP therapy to hospitalized and early-stage disease patients (5). A recent systematic review and meta-analysis showed that convalescent plasma treatment was not significantly associated with a decrease in all-cause mortality (6). Since the level of evidence of the studies is low to moderate, more studies are needed on this subject.

In this study, we aimed to reveal the efficacy of convalescent plasma therapy, which we used in patients with COVID-19 infection who developed acute respiratory distress syndrome (ARDS) followed in our intensive care unit (ICU), on mortality and the factors affecting it.

MATERIAL AND METHOD

Ethical approval was obtained from the University of Health Sciences Hamidiye Clinical Researches Ethics Committee (Date: 27.02.2020, Decision No: 2020.02.27-17). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data including patients' age, clinical, biochemical parameters were extracted from the institutional database. The data (demographic characteristics, amount of CP used, PaO_2/FiO_2, leukocyte, neutrophil, lymphocyte, D-Dimer, C-reactive protein (CRP), procalcitonin, ferritin values, and clinical findings) of 79 patients who were hospitalized in the Level 3 Anesthesiology and Reanimation ICU between 20 March and 20 October 2020 with the diagnosis of COVID-19 and received CP treatment were analyzed retrospectively. Laboratory data before and 48 hours after CP transfusion were used in the study. Initial transfusion data were based on patients who had more than one transfusion.

Patients with COVID-19 pneumonia between the ages of 18 and 90 who were hospitalized in the Sultan 2. Abdulhamid Han Training and Research Hospital COVID-19 ICU and were diagnosed with COVID-19 by polymerase chain reaction (PCR) were included in the study. Patients who were pregnant or breastfeeding, had immunoglobulin allergy, had a low IgA titer (<70 mg/dl), were diagnosed as immunodeficiency, and had undergone chemotherapy for the last 6 months were excluded from the study.

Donor assessments were carried out in compliance with the Republic of Turkey, Ministry of Health, and Donor Eligibility Criteria for COVID-19 Convalescent Plasma (7). The criteria were as follows: evidence of COVID-19 documented by a laboratory or serology test; resolution of symptoms at least 14 days and maximum 3 months before donation and at least 2 negative PCR test results for COVID-19 or have passed 28 days after clinical improvement. As of May 2020, donors' neutralizing antibody (anti-spike IgG) levels were routinely measured whose neutralizing titer was higher than 1/80 were accepted as immune plasma donors. All of the CPs used were obtained by the apheresis method. CPs were processed for pathogen inactivation after collection and then frozen in 200 ml (1 unit) packages. Informed consent was obtained from both the donor and the patients. An ABO compatible CP request was made for all patients hospitalized in the intensive care unit due to COVID-19 pneumonia, with a PaO_2/FiO_2 ratio < 180, and without pregnancy or selective IgA deficiency. However, due to the shortage of supply in some blood groups, not every CP request could be met. The standard dose used for each patient was calculated as 3-4 ml/kg and was used at doses of 200 or 400 milliliters per day with intervals of 24-48 hours. In total, a maximum of 4 doses (800 milliliters) was used for one patient. The decision regarding the total dose given to the patient was made by considering the patient's clinical status and oxygen needs, and CP treatment was repeated in patients with no decrease in oxygen needs (PaO_2/FiO_2 ratio > 180).

Statistical analyses were performed using IBM SPSS Statistics 26 software (IBM Corp., Armonk, NY). Descriptive statistics of the variables (frequency, percentage, mean, standard deviation, minimum, maximum) were calculated. The effects of age and gender, WBC, neutrophil/lymphocyte ratio, ferritin, CRP, procalcitonin, and D-Dimer variables on mortality were measured by logistic regression analysis. Wilcoxon test was used to determine the difference between the parameters measured before and after CP transfusion. All analyzes were evaluated at the 95% confidence interval, and significance was evaluated at the $p < 0.05$ level.

RESULTS

In this study, records of a total of 79 patients who received CP treatment were analyzed. The mean age of the patients was 66.1±12.8 years. 52 (65.8%) of the patients included in the study were male. The mean duration of ICU stay of the patients was 11.97±7.47. The shortest hospital stay was 5 days and the longest 53 days. There was at least one concomitant chronic disease in 76 (96.2%) of the patients. The most common accompanied comorbidity was hypertension (N:40, 50.6%) and with decreasing frequency diabetes mellitus (N:26, 32.9%), chronic obstructive pulmonary disease (N:16, 20%), cancer (N:14, 17.7%), coronary artery disease (N:11, 13.9%), kidney disease (N:10, 12.7%), cerebrovascular disease (N:6, 7.6%), and liver disease (N:5, 6.3%) (**Table 1**).

Table 1. Demographic data and clinical characteristics of the patients

	N	Mean±SD	Minimum-Maximum	%
Age (years)	----	66.1 ±12.8	36- 89	----
Gender (F/ M)	27/52	----	----	34.2/65.8
Total number of patients receiving CP	79	----	----	----
Total amount of CP used (Units)	166	2.1 (per person)	1- 4	----
The number of days of hospitalization in ICU	----	11.97±7.47	5 -53	----
The interval between COVID-19 symptoms and CP transfusion (days)	----	13.45±3.6	7- 26	----
Patients under invasive-MV (Before CP/ After CP*)	38/40	----	----	48.1/50.6
Mortality (F/M)	29 (9/20)	----	----	36.7 (11.4/25.3)
Coexisting diseases	N:76			96.2%
Hypertension	40			50.6
Cerebrovascular disease	6			7.6
Coronary artery disease	11			13.9
Diabetes	26			32.9
Cancer	14			17.7
Liver disease	5			6.3
Chronic obstructive lung disease	16			20
Kidney disease	10			12.7

P: Convalescent plasma, N: Number, SD: Standard deviation, F: Female, M: Male, ICU: Intensive care unit, MV: Mechanical ventilation, *Values measured 48 hours after transfusion.

A total of 166 units of CP was used during the study period. No CP-related adverse effects were observed in any of the patients. While an average of 2.1 units of CP was used per patient, a maximum of 4 units of CP was used per patient (**Table 1**). CPs were used a mean of 13.45±3.6 days after the onset of symptoms of the disease. CP was used at the earliest 7 days after symptom onset and the latest 26 days later (**Figure 1**). 15.2% discharge and 31.6% death were observed in patients who received the first CP infusion 14 days after the onset of symptoms, while 48.1% discharge and 5.1% death were observed in patients who received CP infusion before 14 days (**Figure 2**). All patients with indications for convalescent plasma therapy were included in the study. While 38 (48.1%) patients were under treatment with invasive mechanical ventilation (MV) before transfusion, 40 (50.6%) patients were under invasive-MV treatment 48 hours after transfusion. Mortality was observed in 29 (36.7%) of the patients who had CP. Mortality by gender was higher in male patients (38.5%) than in female patients (33.3%) (**Figure 3**).

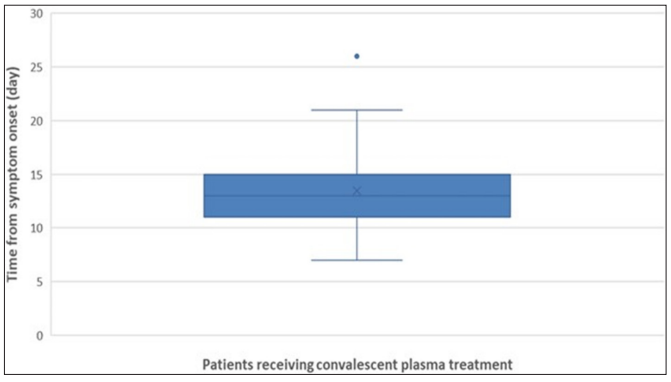

Figure 1. Time interval when patients received first convalescent plasma therapy by symptom onset

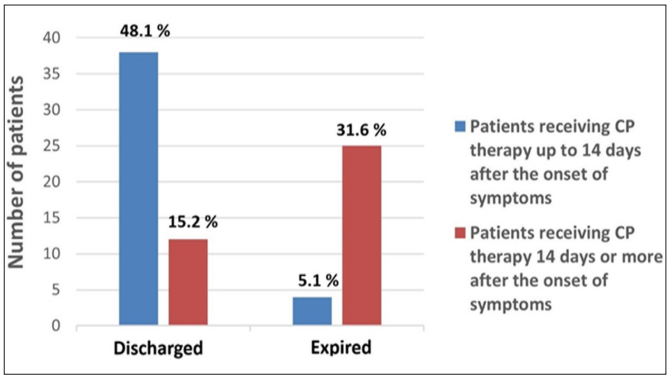

Figure 2. Number of the patients receiving first convalescent plasma therapy by time (day 14) of symptom onset

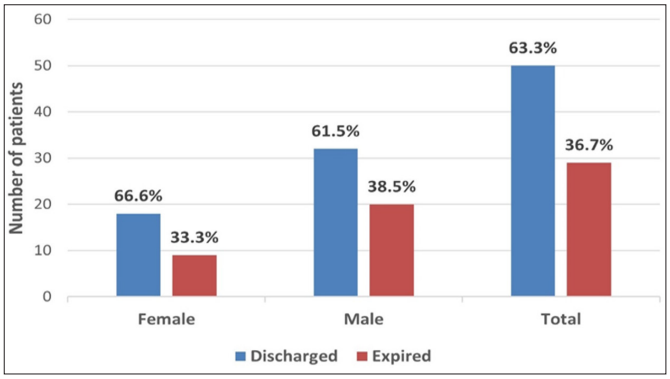

Figure 3. Discharge status of the patients receiving convalescent plasma (CP) therapy.

When the clinical and laboratory characteristics of the patients before and after CP transfusion were compared statistically; No significant difference was detected in terms of oxygenation (PaO_2/FiO_2), Sequential Organ Failure Assessment (SOFA) score, neutrophil, leukocyte, lymphocyte, procalcitonin, D-dimer, ferritin, and CRP values (**Table 2**).

Table 2. Clinical and laboratory characteristics of patients before and after CP transfusion

	Before CP Mean±SD	After CP * Mean±SD	P-value
PaO_2/FiO_2 (NR>300)	139.6±84.9	125.2±82.5	0.850
SOFA score	6.0±3.4	6.2±3.7	0.249
Neutrophil (10^3/mcL) (NR: 1.5 – 8.0)	8.62±4.31	9.23±3.14	0.434
Leukocyte (10^3/mcL) (NR: 4.0- 11.0)	11.15±5.41	11.98±5.04	0.621
Lymphocyte (10^3/mcL) (NR: 1.5- 4.5)	0.76±0.62	0.80±0.64	0.582
Procalcitonin (ng/ml) (NR ≤ 0.05)	0.16±0.23	0.17±0.24	0.357
D-Dimer (ng/ml) (NR ≤ 500)	1520±1955	1552±1385	0.568
Ferritin (ng/ml) (NR: 20-400)	660±454	708±476	0.671
CRP (mg/L) (NR: 0.0- 5.0)	78.6±60.0	65.6±65.4	0.406

SOFA: Sequential Organ Failure Assessment, CRP: C-Reactive Protein, NR: Normal Range, *Values measured 48 hours after transfusion.

The age, gender, number of comorbidities, the first day of CP infusion according to the time of symptom onset, the average amount of CP used, the pre-transfusion PaO_2/FiO_2 ratio, and post-transfusion laboratory data of the deceased and surviving patients were compared with each other and a logistic regression analysis was performed to investigate the relationship with mortality. It was determined that the patient age (p=0.041), neutrophil/lymphocyte ratio (NLR) (p=0.004), CRP value (p=0.002), the number of comorbidities (p<0.001), PaO_2/FiO_2 ratio (p=0.005), and the first day of CP infusion (p<0.001) had a statistically significant effect on mortality. A single unit increase in age, neutrophil/lymphocyte ratio, CRP, the number of comorbidities, PaO_2/FiO_2 ratio, and the first day of CP infusion was found to increase mortality 1.041, 1.071, 1.012, 5.373, 0.990, and 2.064 times, respectively, in a statistically significant manner.

There was no statistically significant effect of gender, mean CP volume used (ml), leukocyte, ferritin, procalcitonin, and D-dimer values on mortality (p>0.05). Although not statistically significant, men had a 0.456 unit higher risk of death than women (**Table 3**).

DISCUSSION

Worldwide, extensive efforts have been made to find effective treatment and prevention agents after facing the SARS-CoV-2 pandemic. Vaccine applications, which are the most important preventive agents, continue rapidly and as of December 2021, 54.5% of the world population has been vaccinated (7). However, despite these efforts, new cases of COVID-19 who are treated in hospital due to new mutagen strains or insufficient antibody response are reported. For this reason, in parallel with the vaccine studies, the search for effective solutions in the treatment continues. One of these treatment modalities is CP treatment, which is a passive immunization, by administering the antibody-rich plasma from recovered patients to the patients after processing. Neutralizing antibodies are the key factor here, preventing the virus from entering cells by binding, regulation of the immune system, phagocytosis, and viral clearance by cells of the immune system, thus shortening the duration of viremia. The history of passive antibody transfer dates back to the 1890s when antibodies were used to protect against bacterial toxins before antimicrobial agents were discovered (8). Since then, CP obtained from recovered

Table 3. Comparison of clinical and laboratory characteristics of the patients according to the outcome

Characteristic	Discharged (n=50)	Expired (n=29)	P value	Logistic regression P value
Age (year)	64.88±13.11	69.07±11.01	0.040*	0.041*
Gender (F/M)	18/32	9/20	0.123	0.456
Neu/Lymph #	31.0±30.3	68.1±49.2	0.007*	0.004*
Leukocyte (10^3/mcL) #	10.52±5.94	15.05±13.49	0.236	0.192
CRP (mg/l) #	86.93±70.58	123.54±62.79	0.006*	0.002*
Procalcitonin (ng/ml) #	2.84±9.13	2.98±4.7	0.463	0.290
Ferritin (ng/ml) #	2422±4631	4105±5837	0.471	0.654
D-Dimer (ng/ml) #	1991±3524	2617±2401	0.169	0.078
The number of comorbidities	1.28±0.73	2.21±0.86	<0.001**	<0.001**
PaO_2/FiO_2 ratio before infusion	162.42±91.1	100.34±55.29	0.01*	0.005*
Mean CP volume (ml)	416±179.98	427.58±237.39	0.81	0.271
Mean day of CP İnfusion (day)	11.7±2.32	16.83±3.35	<0.001**	<0.001**

Neu/Lymph: Neutrophil/Lymphocyte, F: Female, M: Male, CRP: C-reactive protein, CP: Convalescent plasma, # post-transfusion laboratory values, * P < 0.05, **P <0.001

patients has been used as a treatment modality against various infectious pathogens, and varying degrees of clinical efficacy has been achieved, especially in viral infections (9,10).

Based on the experience, the use of CP in the treatment of patients infected with COVID-19 has been suggested at the expert level, and it has been stated that CP therapy will provide potential clinical benefits (11-12). In the Interim Position Paper published by the World Health Organization (WHO) on January 28, 2020, it was stated that immune plasma, serum, or immunoglobulin concentrates could also be used for the SARS-CoV-2 virus, as was applied previously in the MERS epidemic (13).

In our country, CP has started to be obtained from people who have had a COVID-19 infection since April 7, 2020, and 166 units of CP were applied to 79 patients in our ICU until October 2020, and a discharge rate of 63.3% was achieved. In a randomized controlled study conducted by Li et al. (4) in 103 life-threatening COVID-19 patients, CPs with a high neutralizing antibody titer (at least 1:640 and higher) were used in patients on average 14 days after the onset of symptoms, and a mortality rate of 29% in the group receiving CP was found. Similarly, in our patient group, CP was used an average of 13.45±3.6 days after the onset of symptoms, but the mortality rate was higher. We think that this difference is due to the presence of comorbidity in 96.2% of the patients in our study group and the fact that donor plasmas with neutralizing antibody levels of at least 1:80 and above were used in this study.

However, Li et al. (4) did not find a significant difference in 28-day mortality in patients receiving CP therapy added to standard therapy compared with the standard therapy and reported that this may be related to the timing of CP therapy. In a study in which Spironolactone, a potassium-sparing diuretic, was added to the standard treatment of 30 patients hospitalized in the ICU due to COVID-19 and compared with the control group receiving standard treatment, less mortality was observed in the treatment group, and the mortality rate of the treatment group was 46% (14). This rate was found to be higher than the mortality rate of our CP treatment group (36.7%) in this study. In a recent meta-analysis, 7 randomized controlled trials were analyzed. Accordingly, it has been reported that CP therapy reduced mortality when used at an early stage, but did not provide any survival benefits at a stage in which patients required advanced supportive treatments. Only short-term clinical improvements such as a decrease in oxygen demand have been observed (6). In our study, it was also found that the number of comorbidities of patients in the survival group was lower and the oxygenation (PaO_2/FiO_2) values were better than the patients who died. In this case, it will be more useful to start CP therapy before the clinical manifestations of patients deteriorate.

Although CP treatment has been used and researched many times in the past, there is still no standard protocol accepted by all authorities regarding the time and amount of CP use. Chen et al. (9) applied CP treatment to SARS patients (n=80) and observed 6.3% mortality in those receiving CP treatment within the first 14 days after the onset of symptoms, and 21.9% mortality in those receiving treatment after 14 days. In our study, the mortality rate was 5.1% for the early period (first 14 days) and 31.6% for the late period. In addition, in this study, there was a statistical difference between the average time of using CP in expired (mean 16.83±3.35 days) and discharged patients (mean 11.7±2.32 days). Also, there was no difference in terms of the amount of plasma used. Thus, it has been observed that applying early-stage CP treatment shows better clinical results in both diseases.

In an observational study involving 351 patients, it was reported that mortality developed less in individuals who were not intubated and received CP within 72 hours of hospitalization (15). Similarly, another observational study reported that lower mortality was observed when CP was given within three days of diagnosis compared to those given four or more days after diagnosis (16). In our country, according to the newly published guideline after October 2020, CP use is recommended in patients diagnosed with COVID-19 within 7 days at the latest after the onset of symptoms and before the need for intensive care develops (17). In our study, CP treatment was applied to patients an average of 13.45±3.6 days after symptom onset. However, findings showing clinical improvement such as a decrease in MV requirement, increase in oxygenation (PaO_2/FiO_2) value, and decrease in the SOFA score could not be detected. These results also support the current studies in the literature and the CP clinical guide currently applied in our country.

Many researchers have reported that high NLR and CRP levels, which reflect an increased inflammatory process, are effective on prognosis in patients with COVID-19 (18,19). Likewise, studies show that advanced age is a risk factor for mortality in COVID-19 disease (20). In our study, it was determined that the age of the patient, NLR, and CRP values were effective on mortality in the logistic regression analysis using age, gender, and laboratory data (NLR, leukocyte, CRP, procalcitonin, ferritin, D-dimer) measured after CP treatment. Likewise, in a study in which the results of patients who used CP in the ICU were included, it was reported that patient age and lymphocyte count were determining factors in mortality, supporting our results (21).

A large number of articles have been published recently reporting the correlation of biochemical parameters such as NLO, leukocyte, CRP, PaO_2/FiO_2 ratio, procalcitonin, ferritin, D-dimer with the progression of the disease in COVID-19 patients (20-27). Some authors also reported these biomarkers involved in inflammation and coagulation processes as independent risk factors in determining the prognosis (26-29). However, since many of these parameters may cause incorrect assessments in patients with comorbidities that have led to multiple organ dysfunction, they alone may not be sufficient to evaluate the effectiveness of treatment. It is necessary to use parameters that also indicate clinical manifestations while evaluating the effectiveness of treatment. For this purpose, SOFA scores are the most commonly used in critically ill patients. Yang et al. (30) reported that the SOFA score can be used to assess the severity and 60-day mortality of COVID-19.

In this study, the clinical and laboratory characteristics of the patients before and 48 hours after CP transfusion were compared statistically and no significant difference was detected. At the same time, the fact that the SOFA score was higher than 5 before CP treatment was the most important indicator of higher mortality. In a study conducted by Erkurt et al. (21) in 26 COVID-19 patients hospitalized in the ICU, the leukocyte, neutrophil, lymphocyte, platelet, CRP, ferritin, LDH, ALT, AST, spO_2, total bilirubin values of the patients before and 7 days after CP treatment were compared and found no significant difference similar to our study. However, the major limitation here is that the anti-cytokine and anti-inflammatory treatments (steroids, tocilizumab, and cytokine filtration) were given to patients for the treatment of the hyperinflammatory response developing in the course of COVID-19 may have affected this result. For this, there is a need for larger randomized controlled studies comparing the treatments given to the patients.

Some undesirable adverse effects can be seen in CP treatment. These are transfusion-related circulatory overload, infections, acute lung injury, serious allergic reactions, antibody-dependent enhancement (ADE), and coagulation disorders (31). No such adverse effects were observed in the patients in our study.

Our study has some limitations. Firstly; our study didn't have a control group with standard therapy and the patients included in our study received at least one or more of the treatments such as antiviral agents, varying doses of steroids, tocilizumab, and Coupled Plasma Filtration Adsorption (CPFA) before CP transfusion. In conclusion, the possibility that these treatment applications may affect the clinical and laboratory data of the patients cannot be excluded. Second, some patients in the study received up to 800 mL of CP transfusion, and the optimal dose for the disease was not planned.

CONCLUSION

As a result, CP can be safely used to treat COVID-19. However, it has been observed that the positive effect of CP treatment is less in patients in patients with advanced age, advanced stage of the disease, progressive deterioration of oxygenation, and a high number of comorbidities. We believe that the addition of CP treatment with a high neutralizing antibody titer to standard COVID-19 treatment in the early stages of the disease may increase the effectiveness of treatment

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences Hamidiye Clinical Researches Ethics Committee (Date: 27.02.2020, Decision No: 2020.02.27-17).

Informed Consent: All patients signed the free and informed consent form.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015; 211: 80-90.
2. Arabi YM, Hajeer AH, Luke T, et al. Feasibility of using convalescent plasma immunotherapy for MERS-CoV infection. Saudi Arabia. Emerg Infect Dis 2016; 22: 1554-61.
3. Van Griensven J, De Weiggheleire A, Delamou A, et al. The use of ebola convalescent plasma to treat ebola virus disease in resource-constrained settings: a perspective from the field. Clin Infect Dis 2016; 62: 69-74.
4. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020; 324: 460-70.
5. U.S Food & Drug Administration Recommendations for Investigational COVID-19 Convalescent Plasma. Available from: https://www.fda.gov/vaccines-blood-biologics/ investigational-new-drug-applications-inds-cber-regulated-products/ recommendations-investigational-covid-19-convalescent-plasma [accessed 11 September 2021]
6. Janiaud P, Axfors C, Schmitt AM, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. JAMA 2021; 325: 1185-95.
7. Our World in data. Coronavirus (COVID-19) vaccinations. https://ourworldindata.org/covid-vaccinations [accessed 01 December 2021]

8. Casadevall A, Dadachova E, Pirofski LA. Passive antibody therapy for infectious diseases. Nat Rev Microbiol 2004; 2: 695–703.
9. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005; 24: 44–6.
10. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015; 211: 80–90.
11. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest 2020; 130: 1545-8.
12. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 2020; 130: 2757-65.
13. WHO Blood Regulators Network (BRN), "Interim Position Paper on blood regulatory response to the evolving out-break of the 2019 novel coronavirus SARS-CoV-2." http://www.transfusion.ru/2020/04-03-3.pdf [accessed 19 September 2021]
14. Ersoy A, Güven BB, Ertürk T et al. Assessment of the efficacy of spironolactone for COVID-19 ARDS patients. Aydın Sağlık Dergisi 2021; 7: 191-209
15. Salazar E, Christensen PA, Graviss EA, et al. Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG. Am J Pathol 2021; 191: 90-107.
16. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. Preprint. medRxiv 2020; 2020.08.12.20169359.
17. Covıd-19 İmmün (Konvalesan) Plazma Tedarik ve Klinik Kullanım Rehberi 2020. Available from: https://shgmkanhizmetleridb.saglik.gov.tr/Eklenti/39167/0/covid-19-immun-plazma-rehberi-v5.pdf [accessed 11 September 2021]
18. Lagunas-Rangel FA. Neutrophil-to lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID19): A meta-analysis. J Med Virol 2020; 92: 1733-4.
19. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Maladies Infect 2020; 50: 332-3.
20. Albitar O, Ballouze R, Ooi JP, Sheikh Ghadzi SM. Risk factors for mortality among COVID-19 patients. Diabetes Res Clin Pract 2020; 166: 108293.
21. Erkurt MA, Sarici A, Berber İ, Kuku İ, Kaya E, Özgül M. Life-saving effect of convalescent plasma treatment in covid-19 disease: Clinical trial from eastern Anatolia. Transfus Apher Sci 2020; 59: 102867.
22. Roback JD, Guarner J. Convalescent plasma to treat COVID-19: possibilities and challenges. JAMA 2020; 323: 1561-2.
23. Klassen SA, Senefeld JW, Senese KA, et al. Convalescent plasma therapy for COVID-19: a graphical mosaic of the worldwide evidence. Front Med (Lausanne) 2021; 8: 684151.
24. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 2020; 57: 389-99.
25. Yufei Y, Mingli L, Xuejiao L, et al. Utility of the neutrophil-to-lymphocyte ratio and C-reactive protein level for coronavirus disease 2019 (COVID-19). Scand J Clin Lab Invest 2020; 80: 536-40.
26. Gu Y, Wang D, Chen C, et al. PaO_2/FiO_2 and IL-6 are risk factors of mortality for intensive care COVID-19 patients. Sci Rep 11, 7334 (2021). https://doi.org/10.1038/s41598-021-86676-3
27. Şahin Özdemirel T, Akkurt ES, Ertan Ö, Gökler ME, Akıncı Özyürek B. Complications with moderate-to-severe COVID-19 during hospital admissions in patients with pneumonia. J Health Sci Med 2021; 4: 766-71.
28. Güngörer B. Baseline demographic, clinical and laboratory risk factors for predicting admission to intensive care unit in patients diagnosed with COVID-19 in the emergency department. Anatolian Curr Med J 2021; 3; 279-83
29. Ertan Ö, Akkurt ES, Şahin Özdemirel T, Akıncı Özyürek B. A rare case: acute ischemic stroke that developed in a case with severe COVID-19 pneumonia. Anatolian Curr Med J 2021; 3; 256-8
30. Yang Z, Hu Q, Huang F, Xiong S, Sun Y. The prognostic value of the SOFA score in patients with COVID-19: A retrospective, observational study. Medicine (Baltimore) 2021; 100:e26900.
31. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest 2020; 130: 4791-7.

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The effect of the COVID-19 pandemic on the increase of hyperlipidemia and metabolic syndrome in the Turkish population: a retrospective study

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ABSTRACT

Aim: With the Coronavirus Disease 2019 (COVID-19) pandemic starting in late 2019 and continuing into 2020, permanent or periodic quarantine processes and curfews have been implemented. The objective of the study was to investigate the impact of extended quarantine processes during the pandemic on the development of metabolic syndrome (MET-S) due to physical inactivity.

Material and Method: This retrospective study consists of two groups. The first group consists of patients who applied to our hospital in the 12 months preceding the pandemic. The second group consists of the same patients who applied to the same hospital within 12 months of the onset of the pandemic. A total of 44,024 participants who had lab data prior to and during the pandemic were included in the study. Fasting plasma glucose (FPG), Triglyceride (TRIG), Total Cholesterol (T-Chol), High Density Lipoprotein-Cholesterol (HDL-C), Low Density Lipoprotein-Cholesterol (LDL-C) levels and demographic characteristics of the patients were recorded. The test averages were compared between the two groups and their effects on the development of MET-S were subjected to statistical analysis.

Results: When we compared our patients' HDL-C, FPG and TRIG levels measured during the pandemic and the pre-pandemic period, we found a statistically significant increase ($p<0.001$ for all three). We examined whether the COVID-19 pandemic affected the diagnosis criteria for MET-S (TRIG, HDL-C, FPG). The proportion of patients with FPG>100 mg/dL and TRIG>150 mg/dL during the pandemic was statistically significantly higher than during the pre-pandemic period (51.7% vs 45.8%, $p<0.001$; 45.7% vs 42.7%, $p<0.001$).We found that the proportion of patients with HDL-C<50 mg/dL in women and HDL-C<40 mg/dL in men during the pandemic was statistically significantly lower than during the pre-pandemic period (43.7% vs 46.9%, $p<0.001$; 32.4% vs 36.7 $p<0.001$, respectively).

Conclusions: The influence of sedentary living on the development of MET-S, insulin resistance, diabetes mellitus and cardiovascular diseases is known. The levels of FPG, TRIG and HDL-C constitute three of the five diagnostic criteria of MET-S, and abnormal changes in these tests are effective in the formation of MET-S. We have detected a significant increase in FPG and TRIG levels in patients due to the COVID-19 pandemic. Thus, we have established that patients became more susceptible to MET-S on the pandemic due to quarantine. On the other hand, there is a need for further research, including waist circumference and blood pressure data, which are included in the diagnostic criteria for MET-S.

Keywords: Hyperlipidemia, metabolic syndrome, pandemic, COVID-19

INTRODUCTION

The SARS-CoV-2 outbreak was referred to as Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). COVID-19 has spread rapidly across many countries and has been officially declared a pandemic by the WHO since March 11, 2020, with thousands of deaths (1). To prevent the spread of this virus, states have chosen quarantine or taken measures that make it mandatory for all citizens to stay at home. As a result, all sports and fitness events were suspended or cancelled. Hyperventilation during physical activities, particularly in group activities, increases the risk of infection, even if the recommended rules of social distance of 1.5 meters are respected. Because it has been reported that droplets of any size can reach up to 7-8 meters in various environmental and

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disease conditions (2). Home quarantine was applied to protect human health and to reduce the spread rate and speed of the disease, but sedentary behaviours such as staying at home for a long time, sitting, lying, playing games, watching TV, using mobile devices were observed to increase, regular physical activity decreased, therefore less energy was spent (3). During the quarantine period, physical inactivity has reached high levels in our society that is not used to exercise (4).

MET-S is a primary and growing public health issue due to global urbanization, excess energy intake, increased obesity and sedentary lifestyles (5). MET-S is a combination of interdependent risk factors associated with cardiovascular disease and diabetes. These factors include dysglycemia, hypertension, low High Density Lipoprotein-Cholesterol (HDL-C) levels and obesity (6). International Diabetes Federation (IDF) has proposed a number of conditions for the diagnosis of metabolic syndrome. These conditions include increased waist circumference (102 cm in men, 88 cm in women), high Triglycerides (TRIG) (≥150 mg/dL), low HDL-C (<40 mg/dL in men, <50 mg/dL in women), high blood pressure (systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg), increased fasting plasma glucose (FPG) (≥100 mg/dL) and are among the diagnostic criteria of MET-S (7).

Both genetic and acquired factors play a role in each of these conditions. Clinical and epidemiological research shows that obesity is highly associated with cardiovascular risk factors. Fatty tissue is recognized as a source of many potentially pathogenic molecules which are highly unesterified fatty acids, cytokines (tumor necrosis factor-α), resistin, adiponectin, Leptin and Plasminogen Activator Inhibitor (PAI-1). Visceral fatty tissue can be particularly active in the production of most of these factors. However, the mechanisms underlying the association between abdominal lipoidosis (in particular visceral adiposity) and MET-S are not fully understood (8). Exercise is an important element in treating metabolic syndrome. Not only does exercise improve the plasma lipid profile (increased TRIG and decreased HDL-C ratios), it also has positive effects on other risk factors (9). Physical exercise has been shown to reduce skeletal muscle lipid levels and insulin resistance, regardless of Body Mass Index (BMI) (10, 11). Regular exercise has been shown to increase insulin sensitivity, lower plasma TRIG levels and reduce cardiovascular morbidity and mortality (12). Studies on the endocrinological and metabolic effects of exercise have shown that physical exercise increases the use of blood sugar and free fatty acids in the muscles and reduces blood sugar levels in well-controlled diabetic patients. Sustained, light and regular jogging increases the effect of insulin on carbohydrate and lipid metabolism without affecting BMI or maximum oxygen use (13-15).

Since our current data do not include information on waist circumference and arterial blood pressure, we wanted to demonstrate statistically the effect of changes in FPG, HDL-C and TRIG values on the development of MET-S.

In this study, we explained the effect of long quarantine processes on the lipid profile of a particular society in the pandemic and its contribution to the development of MET-S.

MATERIAL AND METHOD

This retrospective study received ethics committee approval of Hitit Univesity Faculty of Medicine Clinical Studies Ethics Committee (Date: 28/04/2021, Decision No: 2021-53). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The hospital data used in this study covers the 12-months period before and after the COVID-19 pandemic was declared by the WHO. Demographic information, lipid profil and fasting plasma glucose values of 214.112 patients admitted to our hospital on an outpatient basis before (2019-12 months) and during the pandemic (2020-12 months) were recorded. Patients over the age of 18 who had been admitted to the outpatient clinic were included in the study. In our study, to reduce the effect of errors in analytical, fasting blood glucose >50 mg/dl, total cholesterol (T-Chol)>30 mg/dl, Triglycerides>20 mg/dl, LDL cholesterol (LDL-C)>20 mg/dl and HDL cholesterol>10 mg/dl were included in the study. Patients admitted to the outpatient clinic of obesity, endocrinology, oncology, diabetes, pediatrics and pediatrics surgery were excluded from the study. Of these patients; 44024 of whom, had laboratory data both before and during pandemic period were included in the study. The study was designed to have two groups. The first group includes outpatients who were admitted to our hospital within 12 months before the pandemic. The second group includes the same patients who were admitted to our hospital on an outpatient basis within a 12-month period after the pandemic began. The Metabolic syndrome diagnostic criteria determined by IDF were based on the study (7).

Laboratory Analysis

The FPG, T-Chol, LDL-C and HDL-C tests used in the present study were performed in the Beckman Coulter AU5800 (Beckman Coulter, Inc, CA, USA) clinical chemistry autoanalyzer in the medical biochemistry laboratory.

Statistical Analysis

Statistical analysis was performed using the SPSS software package (SPSS for Windows-Version 20.0; IBM Corporation, Armonk, NY, USA). Results were taken as mean ± standard

deviation for variables with normal distribution. McNemar test was used to determine the differences between two related groups (year). Paired t-test was used to compare mean values between two related samples. p<0.05 values were considered statistically significant.

RESULTS

The number of patients whose lipid profile and FPG values were measured both in the 12-month period before the pandemic (2019) and in the first 12 months (2020) from the onset of the pandemic on March 11, 2020, their distribution by gender and average age are shown in **Table 1**. The measured FPG and lipid profile values of the patients who applied to our hospital both in the 12-month period before the pandemic (2019) and in the first 12 months (2020) from the onset of the pandemic on March 11, 2020 were compared (**Table 2**). A statistically significant increase was detected in patients' HDL-C, FPG and TRIG levels measured during the pandemic and the pre-pandemic period (12 months before), (p<0.001 for all three). In this study, we have also examined whether the COVID-19 pandemic affected the diagnosis criteria for metabolic syndrome (TRIG, HDL-C, FPG) (**Table 3**). The rate of patients with a TRIG >150 mg/dL, one of the diagnostic parameters of metabolic syndrome, was 45.7% during the pandemic period compared to 42.7% in the pre-pandemic period. This rate was increased statistically significantly during the pandemic period (p<0.001)(**Figure 1**). The rate of patients with a FPG >100 mg/dL, one of the diagnostic parameters of metabolic syndrome, was 51.7% during the pandemic period compared to 45.8% in the pre-pandemic period. This rate was increased statistically significantly during the pandemic period (p<0.001) (**Figure 2**). The rate of patients with a HDL-C<50 mg/dL, one of the diagnostic parameters of metabolic syndrome, was 43.7% during the pandemic period compared to 46.9% in the pre-pandemic period. This rate was statistically decreased during the pandemic (p<0.001) (**Figure 3**). The rate of patients with a HDL-C<40 mg/dL, one of the diagnostic parameters of metabolic syndrome, was 32.4% during the pandemic period compared to 36.7% in the pre-pandemic period. This rate was statistically decreased during the pandemic (p<0.001) (**Figure 4**).

Table 1. Demographic characteristics of the patients and number of the measured tests

	Number of female	Number of male	Mean age of women	Mean age of men	Overall mean age	P valuea
FPG	26595	17429	53.30 16.19	59.48±15.61	55.35±16.71	<0.001*
TRIG	13136	9912	55.08±15.28	58.51±15.19	56.55±15.33	<0.001*
T-Chol	13215	9987	55.01±15.30	58.48±15.18	56.51±15.34	<0.001*
HDL-C	12790	9738	55.34±15.12	58.71±14.99	56.8±15.15	<0.001*
LDL-C	20315	14270	55.34±16.04	58.52±16.18	56.65±16.17	<0.001*

[a]Independent t test, *Significance for 0.05, Abbreviations: FPG: Fasting Plasma Glucose, TRIG: Triglyseride, T-Chol: Total Cholesterol, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol

Table 2. Comparison of lipid profile and FPG values of patients admitted to the hospital both in the 12-month period before and in the first 12 months the pandemic

	Pre-pandemic Period (Mean±SD)	Pandemic period (Mean±SD)	[b]P value
HDL-C (n=22468)	47.86±11.37	48.96±11.87	<0.001*
Female (n=12730)	51.29±11.46	52.51±12.00	<0.001*
Male (n=9738)	43.38±9.57	44.31±9.93	<0.001*
LDL-C (n=34585)	122.4±39.03	122.48±57.70	0.716
Female (n=20315)	126.44±39.50	121.07±56.41	<0.001*
Male (n=14270)	116.52±37.59	124.50±59.41	<0.001*
FPG (n=44024)	115.46±53.46	119.45±54.70	<0.001*
Female (n=26595)	112.75±50.98	116.72±52.95	<0.001*
Male (n=17429)	119.61±56.80	123.61±57.01	<0.001*
TRIG (n=23048)	165.06±127.69	171.38±131.39	<0.001*
Female (n=13136)	159.68±118.41	165.98±138.71	<0.001*
Male (n=9912)	172.22±138.71	178.93±137.00	<0.001*
T-Chol (n=23202)	201.60±51.15	199.63±50.82	<0.001*
Female (n=13215)	209.35±51.84	208.16±49.57	0.012*
Male (n=9987)	191.33±48.35	188.36±50.27	0.001*

[b]Paired t-test, *Significance for 0.05, ***Abbreviations:*** HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, FPG: Fasting Plasma Glucose, TRIG: Triglyseride, T-Chol: Total Cholesterol

Table 3. Effect of pandemic period on metabolic syndrome diagnostic criteria

Metabolic syndrome diagnostic criteria (IDF)	Pre-pandemic period (2019)number and percentage of patients	Pandemic period(2020) number and percentage of patients	P value [c]
FPG >100 mg/dL	20197 45.8%	22791 51.7%	0.001*
TRIG >150 mg/dL	9861 42.7%	10536 45.7%	0.001*
HDL-C <50 mg/dL (Female)	5973 46.9%	5558 43.7%	0.001*
HDL-C <40 mg/dL (Male)	3569 36.7%	3157 32.4%	0.001*

[c]Mc Nemar Test, *Significance for 0.05, ***Abbreviations:*** IDF: International Diabetes Federation, FPG: Fasting Plasma Glucose, TRIG: Triglyseride, HDL-C: High Density Lipoprotein Cholesterol.

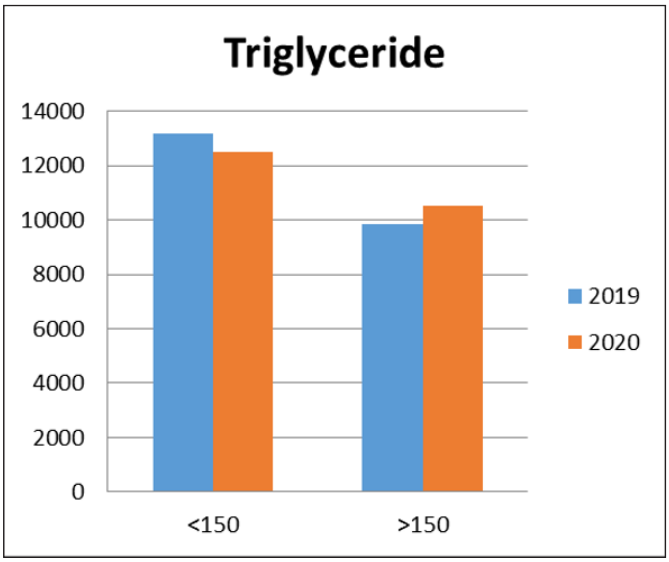

Figure 1. Contribution of pandemic on the development of metabolic syndrome based on triglyceride value

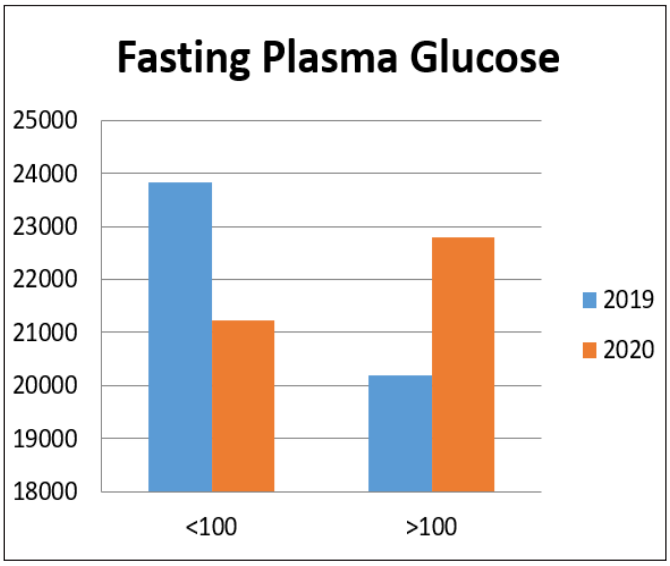

Figure 2. Contribution of pandemic on the development of metabolic syndrome based on FPG value

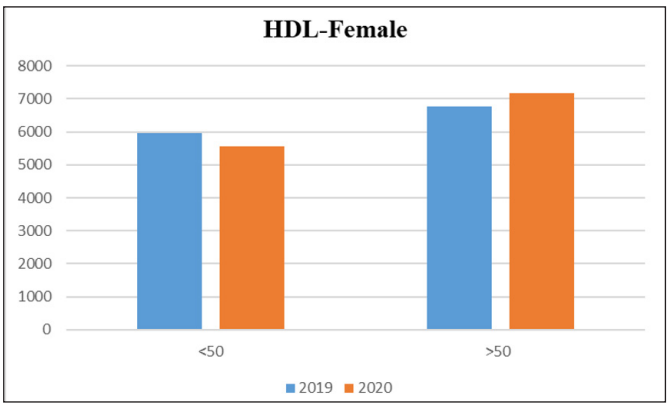

Figure 3. Contribution of pandemic on the development of metabolic syndrome based on HDL-C in female patients

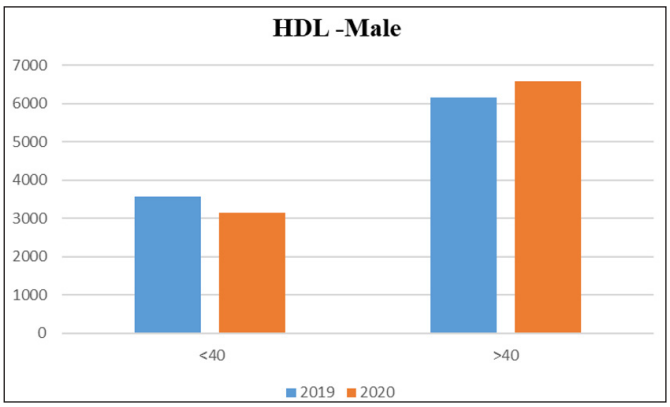

Figure 4. Contribution of pandemic on the development of metabolic syndrome based on HDL-C in men patients

DISCUSSION

During the period of social isolation adopted globally to control the spread of COVID-19, global levels of physical activity have decreased significantly. This social isolation has metabolic effects in patients with metabolic diseases or those at risk for this disease, particularly in patients with obesity and type 2 diabetes mellitus (T2DM). Although isolation measures are important for containing the virus, they may have exacerbated an ancient pandemic ('physical inactivity') (16). WHO has provided clear guidance on the minimum level of physical activity required to maintain good health and fitness. For example, recent statistics indicate that adults between the ages of 18 and 64, the age group most affected by COVID-19 (representing over 70% of all serious cases) need to have at least 150 minutes of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity per week (17,18). Time spent while sitting seems to have harmful effects, even in those who meet current physical activity guidelines. However, health problems are less common among physically active individuals than their inactive counterparts (19-21). We anticipate increased FPG and lipid profile (LDL-C, T-Chol and TRIG) and decreased levels of HDL-C due to inactivity during the pandemic. Gennuso et al. (22) found that total sedentary time was associated with an increase in the probability of developing MET-S, and moderate and vigorous physical activity was associated with a decrease in the rate of MET-S development. Van der Berg et al. (23) stated that an additional hour of inactivity increased the likelihood of developing T2DM and MET-S by 22% and 39% respectively. The inability to take a regular walk from home as a result of a strict quarantine increases the risk of many serious diseases such as diabetes, cancer, osteoporosis and cardiovascular disease (24). Short-term bed rest studies, used as a model of sedentary behaviour, showed deteriorations in glucose metabolism and insulin sensitivity (25). In a study conducted by Olsen et al. (26), they reported that a decrease in daily steps from 6200 to 1400 increased insulin resistance among healthy people. In addition to physical inactivity, the COVID-19 pandemic has also caused excessive energy intake.

Physical inactivity and excessive energy intake are often combined and contribute to the epidemic of obesity and type 2 diabetes (27). In a study conducted by Mikus et al. (28) in healthy young adults, they proved that reduced physical activity for three days caused an increase in insulin and C-peptide levels in the OGTT response, and also increased glycemic fluctuations. It is well known that such a sedentary lifestyle, such as desk job, watching TV, and sitting, is associated with an increase in mortality and morbidity from all causes (MET-S, cardiovascular disease, etc.) (27, 29, 30). In their study, Ekelund et al. (31) demonstrated that any intensity of physical activity and less sedentary time are associated with a reduced risk of premature death in middle-aged and older adults. Similar to the above studies, fasting blood glucose levels were also found to be elevated in our study due to the physical inactivity during the COVID-19 pandemic. This showed us that the pandemic made a statistically significant contribution to the diagnosis of metabolic syndrome by increasing FPG levels (**Table 2**). Prolonged physical inactivity also affects lipid metabolism. Indeed, inactivity leads to insulin resistance and dyslipidemia, i.e to an increase in TRIG rates associated with a decrease in HDL-C concentration. Mazzucco et al. (32) showed that inactivity following bed rest reduced the ratio of HDL-C to non-HDL-C. Being physically active is associated with a better anthropometric and metabolic health profile, whereas a sedentary life regardless of activity (Light Movers) is associated with lower HDL-C (a traditional cardiovascular risk factor) (33). Dixon et al. (34) conducted a study in which individuals had their steps reduced by less than 4,000 steps/day during a week. In this study, they compared lean and overweight people. As a result, they showed that insulin, FPG and TRIG concentrations increased in both groups, and an additional increase in CRP and ALT levels in the overweight group. There were no changes in T-Chol, LDL-C and HDL-C during the study, and no differences occurred between the groups. Bowden Davies et al. (34) found an increase in T-Chol, TRIG and LDL-C values in their study conducted in 45 healthy individuals who had their steps reduced below 1500 per day for 2 weeks. Winn et al. (36) found that there was no significant change in T-Chol, TRIG, HDL-C, LDL-C and oxidized LDL-C after 10 days of step restriction and 800 kcal diet in 10 healthy individuals. Similar to the above studies, we found a statistically significant increase in TG levels during the pandemic (sedentary period) compared to the pre-pandemic (active period) in our study ($p<0.001$) (34, 35). Contrary to the above studies HDL-C levels were higher in the pandemic period (sedentary period) than in the pre-pandemic period, (48.96±11.87 mg/dL and 47.86±11.37 mg/dL, respectively) ($p<0.001$)(32,34). While there was a significant decrease in T-Chol, we found no statistically significant differences in LDL-C levels prior to and during the pandemic (**Table 2**). We observed a statistically significant increase in FPG and TG levels, which are the MET-S criteria of the COVID-19 pandemic (both $p<0.001$). When we consider at the contribution of the pandemic to the diagnosis of MET-S through FPG, the rate of patients with FPG>100 was 51.7% during the pandemic compared to 45.8% in the pre-pandemic period. Still, when we consider at the contribution of the pandemic to the diagnosis of MET-S through TG, the rate of patients with TG>150 was increased to 45.7% during the pandemic compared to 42.7% in the pre-pandemic period. With this study, we demonstrated that the pandemic contributed to the diagnosis of MET-S by causing an increase in FPG and TRIG values. Contrary to these parameters, we found a statistically significant decrease in the ratio of female patients with HDL-C<50 and male patients with HDL-C<40 during the pandemic period (sedentary period) (**Table 3**). Once again, our study has shown that HDL-C values do not contribute to the diagnosis of MET-S during the pandemic.

Limitations: This study has some limitations despite its large sample advantage. As the present study was designed retrospectively, other metabolic syndrome diagnostic criteria such as waist circumference and systolic and diastolic blood pressure values of the patients could not be measured.

CONCLUSION

As a result, we determined that the pandemic contributed to the diagnosis of MET-S by increasing the FPG and TG levels of the patients, but could not contribute to the diagnosis of MET-S by also increasing HDL-C levels. Alternative sports activities in the long quarantine processes caused by the pandemic are of protective importance to prevent the development of obesity and metabolic syndrome. However, there is a need for further research, including waist circumference and blood pressure data, which are included in the diagnostic criteria for MET-S.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit Univesity Faculty of Medicine Clinical Studies Ethics Committee (Date: 28/04/2021, Decision No: 2021-53)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Park SE. Epidemiology, virology, and clinical features of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). Clin Exp Pediatr 2020; 63: 119-24.
2. Bourouiba L. Turbulent gas clouds and respiratory pathogen emissions: potential implications for reducing transmission of COVID-19. JAMA 2020; 323: 1837-8.
3. Gençalp DK. COVID-19 salgını döneminde ilk ve acil yardım öğrencilerinin beslenme alışkanlıkları ve fiziksel aktivite durumlarının değerlendirilmesi. Paramedik ve Acil Sağlık Hizmetleri Derg 2020; 1: 1-15.
4. Caner ZG. Ünal M, Apaydın Z, et al. COVID-19 hastalığı ve ev egzersizlerinin önemi. J Med Sci 2020; 1: 25-33.
5. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014: 943162.
6. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 2009; 120: 1640-5.
7. Alberti KG, Zimmet P, Shaw J. Metabolic Syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006: 23: 469-80.
8. Grundy SM, Hansen B, Smith SC Jr, et al. American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation 2004; 109: 551-6.
9. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 2002; 25: 2165- 71.
10. Sato Y. Diabetes and life-styles: role of physical exercise for primary prevention. Br J Nutr 2000; 84: 187-90.
11. Amati F, Dubé JJ, Alvarez-Carnero E, et al. Skeletal muscle triglycerides, diacylglycerols, and ceramides in insulin resistance: another paradox in endurance-trained athletes? Diabetes 2011; 60: 2588-97.
12. Koplan JP, Dietz WH. Caloric imbalance and public health policy. JAMA 1999; 282: 1579-81.
13. Sato Y, Nagasaki M, Kubota M, Uno T, Nakai N. Clinical aspects of physical exercise for diabetes/metabolic syndrome. Diabetes Res Clin Pract 2007; 77: 87-91.
14. Haram PM, Kemi OJ, Lee SJ, et al. Aerobic interval training vs. continuous moderate exercise in the metabolic syndrome of rats artificially selected for low aerobic capacity. Cardiovasc Res 2009; 81: 723-32.
15. Gutin B, Owens S. The influence of physical activity on cardiometabolic biomarkers in youths: a review. Pediatr Exerc Sci 2011; 23: 169-85.
16. Uyaroğlu OA, Özdede M, Çalık Başaran N, et al. Hyperlipidemia in post-COVID patients; a unique observational followup study on lipid levels in post-COVID patients. J Health Sci Med 2022; 5: 220-6.
17. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239-42.
18. World Health Organization. Physical activity, https://www.who.int/news-room/fact-sheets/detail/physical-activity(2018, accessed 12 March 2020).
19. Bouchard C, Blair SN, Katzmarzyk PT. Less sitting, more physical activity, or higher fitness? Mayo Clin Proc 2015; 90: 1533-40.
20. Wilmot EG, Edwardson CL, Achana FA, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia 2012; 55: 2895-905.
21. Hamilton MT, Hamilton DG, Zderic TW. Sedentary behavior as a mediator of type 2 diabetes. diabetes and physical activity. Med Sport Sci 2014; 60: 11-26.
22. Gennuso KP, Gangnon RE, Thraen-Borowski KM, Colbert LH. Dose–response relationships between sedentary behaviour and the metabolic syndrome and its components. Diabetologia 2015; 58: 485-92.
23. van der Berg JD, Stehouwer CDA, Bosma H, et al. Associations of total amount and patterns of sedentary behaviour with type 2 diabetes and the metabolic syndrome: The Maastricht Study. Diabetologia 2016; 59: 709-18.
24. Lippi G, Henry BM, Sanchis-Gomar F. Physical inactivity and cardiovascular disease at the time of coronavirus disease 2019 (COVID-19). Eur J Preventive Cardiol 2020; 27: 906–8.
25. Hamburg NM, McMackin CJ, Huang AL, et al. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. Arterioscler Thromb Vasc Biol 2007; 27: 2650-6.
26. Olsen RH, Krogh-Madsen R, Thomsen C, Booth FW, Pedersen BK. Metabolic responses to reduced daily steps in healthy nonexercising men. JAMA 2008; 299: 1261-3.
27. Methnani J, Amor D, Yousf N, Bouslama A, Omezzine A, Bouhlel E. Sedentary behavior, exercise and COVID-19: immune and metabolic implications in obesity and its comorbidities. J Sports Med Phys Fitness 2020; 61: 1538-47.
28. Mikus CR, Oberlin DJ, Libla JL, Taylor AM, Booth FW, Thyfault JP. Lowering physical activity impairs glycemic control in healthy volunteers. Med Sci Sports Exerc 2012; 44: 225–31.
29. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. Med Sci Sports Exerc 2009; 41: 998–1005.
30. Van der Ploeg H P, Chey T, Korda RJ, Banks E, Bauman A. Sitting time and all-cause mortality risk in 222 497 Australian adults. Arch Intern Med 2012; 172: 494–500.
31. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose response associations between accelerometry measured physical activity and sedentary time and all cause mortality: Systematic review and harmonised meta-analysis. BMJ 2019; 366: l4570
32. Mazzucco S, Agostini F, Mangogna A, Cattin L, Biolo G. Prolonged inactivity up-regulates cholesteryl ester transfer protein independently of body fat changes in humans. J Clin Endocrinol Metab 2010; 95: 2508–12.
33. Bakrania K, Edwardson CL, Bodicoat DH, et al. Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health in English adults: a cross-sectional analysis of the Health Survey for England. BMC Public Health 2016; 16: 25.
34. Dixon NC, Hurst TL, Talbot DCS, Tyrrell RM, Thompson D. Effect of short-term reduced physical activity on cardiovascular risk factors in active lean and overweight middle-aged men. Metabolism 2013; 62: 361–8.

35. Bowden Davies KA, Sprung VS, Norman JA, et al. Short-term decreased physical activity with increased sedentary behaviour causes metabolic derangements and altered body composition: effects in individuals with and without a first-degree relative with type 2 diabetes. Diabetologia 2018; 61: 1282–94.
36. Winn NC, Pettit-Mee R, Walsh LK, et al. Metabolic implications of diet and energy intake during physical inactivity. Med. Sci. Sports Exerc 2019; 51: 995–1005.

Original Article

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Tranexamic acid in knee arthroplasty: the effect of preoperative intravenous administration of together with postoperative intravenous maintenance and periarticular administration on bleeding, transfusion, and hospitalization time – a retrospective cohort study

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ABSTRACT

Objective: To compare patients who received preoperative intravenous (IV) plus postoperative maintenance IV tranexamic acid (TXA) therapy and perioperative periarticular TXA to those who did not receive TXA during total knee arthroplasty (TKA) in terms of blood loss, transfusion requirements, and length of hospital stay.

Material and Method: Data from 194 patients who underwent TKA between 2016 and 2019 were reviewed. A total of 106 patients were included. Twenty-one patients were male, and 95 were female. The patients were divided into three groups: Group 1 (n=37) that did not receive perioperative TXA, Group 2 (n=35) that received preoperative IV and postoperative maintenance TXA therapy, and Group 3 (n=34) that received preoperative IV and perioperative periarticular TXA. The groups were similar regarding demographic data. Statistical comparisons between the groups were made concerning the decrease in hemoglobin levels on postoperative days 1 and 3, the need for transfusion, and the length of hospital stay.

Results: The mean decrease in hemoglobin on the postoperative first and third days were 1.69(±1.13) and 2.94(±1.14)g/dl, in Group 1, 1.41(±0.99) and 2.44(±1.28)g/dl, in Group 2, and 1.24(±0.83) and 2.21(±0.84)g/dl in Group 3 respectively. The statistical comparison of the hemoglobin decrease revealed a significant difference between Groups 1 and 3 on the postoperative first day($p<0.05$). There was no other significant difference between the remaining group pairs. There was a statistically significant difference in the length of hospital stay and the amount of erythrocyte suspension used between Groups 1 and other groups ($p<0.05$). In Group 1, prolonged wound discharge was observed in four patients. No additional surgical intervention was performed in any of the three groups due to infection, and no vascular thrombosis or embolism was observed.

Conclusion: Our results showed that IV and periarticular TXA applications in TKA effectively reduced bleeding and bleeding-related complications without causing additional complications.

Keywords: Knee arthroplasty, tranexamic acid, transfusion, blood loss, intravenous, periarticular, maintenance therapy

INTRODUCTION

The increase in average human life expectancy, aging population, increased expectations concerning quality of life, and technological developments in orthopedics and traumatology have led to a significant increase in knee arthroplasty procedures. Blood loss during and after joint replacement surgery is one of the most critical problems to be addressed. Up to 1,000 ml of blood is lost during knee arthroplasty surgery, to which approximately 500 ml of unseen loss is added postoperatively (1,2). Therefore, 9-84 % of patients require a blood transfusion after knee arthroplasty surgery (3).

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Blood transfusions carry many risks, with the primary being blood-borne diseases, such as hepatitis B/C and human immunodeficiency virus. As a result of immunomodulation and immunosuppression that can occur after transfusion, postoperative infection rates increase, length of hospital stay is prolonged, recovery and return to function are slowed down, and mortality increases (4). Therefore, it is essential to reduce perioperative blood loss and the need for transfusion (5). In clinical practice, various methods are used to reduce blood loss (6), including antifibrinolytics. Tranexamic acid (TXA) is an antifibrinolytic drug, a synthetic lysine analog that acts as a plasminogen activator inhibitor. There is increasing scientific evidence that TXA, which has long been used to prevent blood loss during cardiothoracic and gynecologic surgery, can reduce perioperative blood loss during joint replacement surgery (7-9). TXA can be administered intravenously or periarticularly. Many studies have shown that both intravenous (IV) and periarticular administration of TXA significantly reduce blood loss while not increasing the risk of deep venous thrombosis (DVT) (10-12).

In the current medical literature, many articles discuss the use of IV and periarticular TXA in knee arthroplasty surgery. However, only a limited number of articles address the efficacy and safety of maintenance therapy with TXA after preoperative and periarticular TXA administration in knee arthroplasty surgery.

In this study, we compared the patients who received preoperative IV plus postoperative IV TXA or preoperative IV plus perioperative periarticular TXA with those who did not receive TXA during total knee arthroplasty (TKA) in terms of blood loss, transfusion requirements, and length of hospital stay.

MATERIAL AND METHOD

The study was carried out with the permission of Gaziosmanpaşa Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.11.2021, Decision No: 372). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective cohort study evaluated data from 194 patients operated on by a single arthroplasty surgeon between 2016 and 2019 with the same type of cruciate ligament preserving prosthesis (Genesis 2, Smith and Nephew, Memphis, TN, USA) diagnosed with primary gonarthrosis, who received preoperative IV TXA plus maintenance TXA for one day postoperatively, preoperative IV TXA plus perioperative periarticular TXA, and who were not administered perioperative TXA were retrospectively studied by reviewing patient records.

Patients with morbid obesity (body mass index > 35, n=21), history of deep vein thrombosis (n=5), renal dysfunction (n=12), cardiac problems (n=10), or rheumatologic diseases (n=8), those using anticoagulants (n=10), and those with severe soft tissue deformities [more than 20° varus (n=11)] or valgus (n=6) deformity, or 15° flexion contracture (n=5)] were excluded from the study.

A total of 106 cases that met the study criteria were included in the sample. Twenty-one of the patients were male, and 95 were female. The mean age was 64.79 (47-89) years.

Spinal or epidural anesthesia was performed in all patients. For prophylaxis, 2 grams of cefazolin sodium was administered intravenously as standard. Cruciate-retaining knee prosthesis was inserted via a parapatellar incision in all patients. For thromboembolism prophylaxis, 0.4 ml of Clexane was administered subcutaneously 12 hours after surgery and continued until ten days after discharge.

The patients in the study were divided into three groups:

- Group 1: surgery was performed with a pneumatic tourniquet without the administration of TXA.
- Group 2: the patients received 10 mg/kg IV TXA in 100 ml saline before incision and the same dose IV as an eight-hour infusion in the second hour after surgery.
- Group 3: the patients received 10 mg/kg IV TXA in 100 ml of physiological saline before incision, and the same dose was applied to the tissue around the joint at the end of surgery.

In Groups 2 and 3, the tourniquet was used only during cementation when the prosthesis was inserted.

A hemoglobin value below 70 mg/dl and a postoperative decrease of 30 mg/dl compared to the preoperative value were used as transfusion indications(13). In addition, changes in hemoglobin levels, length of hospital stay, and patients' blood transfusion requirements were assessed before surgery and on the postoperative first and third days.

Statistical Method: SPSS version 22 for Mac (SPSS Inc., Chicago, IL) was used for the statistical analysis. Mean, standard deviation, median, minimum and maximum values were used as descriptive statistics. The distribution of variables was checked using the Kolmogorov-Smirnov test. One-tailed analysis of variance was used to analyze data with a normal distribution, and the Kruskal-Wallis test was used to analyze data without a normal distribution. A p value of <0.05 was taken as the statistical significance limit.

RESULTS

Table 1 presents the decrease in hemoglobin levels on the postoperative first and third days. There was no statistically significant difference between Groups 1 and 2 and between Groups 2 and 3 in terms of the hemoglobin decrease on the postoperative first day ($p > 0.05$), while a significant difference was found between Groups 1 and 3 ($p < 0.05$) (**Table 2**).

The length of hospital stay of the groups and the number of erythrocyte suspensions applied are shown in Table 1. There was a statistically significant difference between Groups 1 and 2 and between Groups 1 and 3 in terms of the length of hospital stay ($p=0.005$). However, no statistically significant difference between Groups 2 and 3, although the length of hospital stay was lower in Group 2 (**Table 3**). The number of erythrocyte suspensions used statistically significantly differed between Group 1 and the remaining two groups. The number of erythrocyte suspensions used in Group 3 was lower compared to Group 2, albeit with no statistically significant difference (**Table 3**).

Prolonged serous discharge was observed in four patients in the early postoperative period in Group 1 and resolved with dressing control within ten days without the need for additional surgery. None of the patients in any of the groups required second surgery due to bleeding, serous discharge, or infection. No DVT, pulmonary embolism, or cardiac or cerebrovascular embolism was observed in any group.

DISCUSSION

This study compared the patients who received preoperative IV and postoperative IV TXA, preoperative IV, and perioperative periarticular TXA with those who did not receive TXA during TKA in terms of blood loss, transfusion requirements, and length of hospital stay. The decrease in hemoglobin levels was significantly lower in the patients administered periarticular TXA on the first day. Moreover, both TXA-administrated groups provided significantly better results than the non-TXA group in terms of erythrocyte suspension requirement and length of hospital stay. No thromboembolic complication was observed in any of the groups.

Table 1. Demographic data of the groups

	Group 1 (Non-tranexamic acid (n=37)	Group 2 IV tranexamic acid (n=35)	Group 3 Periarticular tranexamic acid (n=34)
Age (years)	65±9.24	65.05±7.77	64.82±6.72
Gender			
Female	30 (81%)	29 (83%)	26 (76%)
Male	7 (19%)	6 (17%)	8 (24%)
Average Hgb decrease on postoperative day 1 (g/dl)	1.69±1.13	1.41±0.99	1.24±0.83
Average Hgb decrease on postoperative day 3 (g/dl)	2.94±1.14	2.44±1.28	2.21±0.84
Average length of hospital stay (days)	5.2 ±1.50	3.77±1	3.88±0.76
Transfusion (U)	1.74±1.06	0.57±0.61	0.72±8.33

IV, intravenous; Hgb, hemoglobin

Table 2. Statistical data on hemoglobin decrease on the postoperative first and third days

Paired-samples Test								
First-day hemoglobin decrease	Paired differences					t	df	Sig. (2-tailed)
	Mean	SD	Std. error mean	95% CI				
				Lower	Upper			
Group 1 vs Group 2	0.240	1.42	0.240	-2.487	7.287	0.998	34	0.325
Group 1 vs Group 3	0.447	1.34	0.299	-0.208	9.149	1.944	33	0.060
Group 2 vs Group 3	0.200	1.24	0.212	-2.329	6.329	0.940	33	0.354
Third-day hemoglobin decrease								
Group 1 vs Group 2	0.422	1.58	0.268	-1.225	9.682	1.576	34	0.124
Group 1 vs Group 3	0.694	1.31	0.225	2.353	11.528	3.079	33	0.004*
Group 2 vs Group 3	0.294	1.57	0.270	-2.256	8.449	1.086	33	0.285

SD, standard deviation; CI, confidence interval; Group 1, non-tranexamic acid; Group 2, intravenous tranexamic acid; Group 3, periarticular tranexamic acid

Table 3. Statistical data on the length of hospital stay and erythrocyte suspension requirements

	Test Statistics[a]					
	Length of hospital stay			Erythrocyte suspension requirement		
	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
Z	-3.747[b]	-3.941[b]	-0.606[c]	-4.191[b]	-3.830[b]	-0.557[c]
Asymp. Sig. (2-tailed)	.000	.000	.000	.000	.000	.557

[a]Wilcoxon signed-ranks test, [b]Based on positive ranks, [c]Based on negative ranks Group 1, non-tranexamic acid; Group 2, intravenous tranexamic acid; Group 3, periarticular tranexamic acid

The use of TXA has recently gained popularity to reduce blood loss and transfusion requirement during knee arthroplasty surgery. Studies on the ideal dose and method of application have occupied an important place in the orthopedic literature in recent years. In this study, we investigated the efficacy of different administration methods of TXA.

Many studies have shown that TXA prevents blood loss in knee arthroplasty. For example, in a meta-analysis, Yang et al. (14) reported that IV TXA administration reduced blood loss by 504 ml transfusion and 1.43 units on average. In our study, we assessed blood loss based on the decrease in the hemoglobin level, which, we believe, is more valuable as a subjective assessment than the need for blood transfusion. In this regard, the statistically significant differences between Group 1 (no TXA), and Group 2 (preoperative TXA plus maintenance therapy) and Group 3 (preoperative IV and perioperative periarticular TXA) demonstrates the efficacy of TXA in preventing blood loss.

Although many studies have shown TXA to be effective in preventing blood loss, which of the administration methods is more effective is still a subject of research. Attempts are being made to increase the efficacy of TXA administered at the onset of anesthesia by different methods. In our study, no significant difference was found between the patients who received a single infusion in addition to the initial infusion and postoperative periarticular TXA. Both methods are effective in reducing the decrease in hemoglobin despite the absence of a tourniquet. This activity increases, especially after the first day. This can be attributed to the continuation of the efficacy of TXA in the postoperative period.

Previous studies have also investigated the efficacy of multiple postoperative TXA infusions (15,16). Tzatraitis et al. (15) found that the third dose of TXA infusion was more effective in maintaining hemoglobin levels. The authors observed a 2.33 mg/dL decrease in hemoglobin in patients who received the third TXA dose. In our study, the hemoglobin decrease was almost the same in both TXA groups. Therefore, it would be beneficial to further investigate whether a third dose of TXA infusion is really necessary.

In a 2017 study by Schnettler et al.(17), the use of tourniquets was reported to increase blood loss. In the current study, the tourniquet was inflated during cementation in Groups 2 and 3, while surgery was performed with a pneumatic tourniquet in Group 1.

, which was determined to be the group with the most negligible blood loss. However, to the best of our knowledge, there is no study on the paradoxical increase in blood loss in patients treated with a tourniquet.

In our study, except for the application of cement, a pneumatic tourniquet was not used in the patients administered TXA, whereas the operations in Group 1 were performed under the tourniquet. We can explain the lack of significant differences in hemoglobin decrease, especially in our measurements on the postoperative first day by the lower intraoperative bleeding in the patients who did not receive TXA. We believe that randomized clinical trials are needed to understand the impact of using a tourniquet on blood loss in the postoperative period.

In a retrospective study published by Saad et al. (18), 54 patients (31 revision knee arthroplasty/23 revision hip arthroplasty) who received 1 g IV TXA before incision and underwent wound closure were hospitalized for an average of 3.48 days postoperatively, and 46 patients who did not receive TXA (23 revision TKA/23 revision THA) were hospitalized for an average of 5.22 days postoperatively. This difference was statistically significant. The authors also reported that the use of TXA significantly reduced the need for postoperative transfusion. In our study, a statistically significant difference was found between Group 1 that did not receive TXA and both TXA-administered groups in terms of the length of hospital stay. However, there was no statistically significant difference between the groups receiving postoperative maintenance TXA and perioperative periarticular TXA.

In this study, we did not encounter any thrombotic complications associated with the use of TXA. The lack of diagnostic studies on thrombotic complications besides clinical evaluation may lead to overlooking subclinical complications. In the meta-analysis by Kerver et al. (19), examining 129 studies with 10,488 cases on the efficacy of TXA on bleeding, it was reported that the effect of TXA use on the incidence of DVT, pulmonary embolism, and myocardial infarction was inconclusive, but TXA statistically significantly reduced patient mortality. We believe that prospective randomized trials to be conducted in future will be helpful in clarifying this issue.

Despite the limitations of our study due to the retrospective design and relatively small number of patients, our results can be considered valuable because there were no differences in age, sex, weight, and preoperative hemoglobin levels between the groups. Standardization was achieved because the patients were operated on by the same surgeon with the same type of prosthesis. Although single-center trials have been shown to have higher treatment efficacy than multicenter trials in randomized clinical trials, there is no reason to believe that this would affects the results of the retrospective evaluation of case series, such as our study (20).

CONCLUSION

The results of this study showed that in TKA, in addition to preoperative IV TXA administration, postoperative IV maintenance therapy and perioperative periarticular TXA administration decreased the amount of bleeding and transfusion requirement during and after surgery and reduced the length of hospital stay. We believe that TXA administration in patients who have safely undergone arthroplasty is beneficial to prevent bleeding, long hospital stay, and transfusion-related complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziosmanpaşa Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.11.2021, Decision No: 372).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Berman AT, Geissele AE, Bosacco SJ. Blood loss with total knee arthroplasty. Clin Orthop Relat Res 1988; 234: 137-8.
2. Sehat KR, Evans R, Newman JH. How much blood is really lost in total knee arthroplasty? Correct blood loss management should take hidden loss into account. Knee 2000; 7: 151-5.
3. Barr PJ, Donnelly M, Cardwell C, et al. Drivers of transfusion decision making and quality of the evidence in orthopedic surgery: a systematic review of the literature. Transfus Med Rev 2011; 25: 304-16.
4. Shander A, Hofmann A, Gombotz H, Theusinger OM, Spahn DR. Estimating the cost of blood: past, present, and future directions. Best Pract Res Clin Anaesthesiol 2007; 21: 271-89.
5. Lemaire R. Strategies for blood management in orthopaedic and trauma surgery. J Bone Joint Surg Br 2008; 90: 1128-36.
6. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. J Am Acad Orthop Surg 2010; 18: 132-8.
7. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs. 1999; 57: 1005-32.
8. Naoulou B, Tsai MC. Efficacy of tranexamic acid in the treatment of idiopathic and non-functional heavy menstrual bleeding: a systematic review. Acta Obstet Gynecol Scand 2012; 91: 529-37.
9. Melvin JS, Stryker LS, Sierra RJ. Tranexamic acid in hip and knee arthroplasty. J Am Acad Orthop Surg 2015; 23: 732-40.
10. Chen JY, Chin PL, Moo IH, et al. Intravenous versus intra-articular tranexamic acid in total knee arthroplasty: a double-blinded randomised controlled noninferiority trial. Knee 2016; 23: 152-6.
11. Goyal N, Chen DB, Harris IA, Rowden NJ, Kirsh G, MacDessi SJ. Intravenous vs intra-articular tranexamic acid in total knee arthroplasty: a randomized, double-blind trial. J Arthroplasty 2017; 32: 28-32.
12. Mi B, Liu G, Zhou W, et al. Intra-articular versus intravenous tranexamic acid application in total knee arthroplasty: a meta-analysis of randomized controlled trials. Arch Orthop Trauma Surg 2017; 137: 997-1009.
13. Liumbruno GM, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Italian Society of Transfusion Medicine and Immunohaematology Working Party. Recommendations for the transfusion management of patients in the peri-operative period. III. The post-operative period. Blood Transfus 2011; 9: 320-35.
14. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am 2012; 94: 1153-9.
15. Tzatzairis T, Drosos GI, Vogiatzaki T, Tilkeridis K, Ververidis A, Kazakos K. Multiple intravenous tranexamic acid doses in total knee arthroplasty without tourniquet: a randomized controlled study. Arch Orthop Trauma Surg 2019; 139: 859-68.
16. Wang D, Wang HY, Luo ZY, Pei FX, Zhou ZK, Zeng WN. Finding the optimal regimen for oral tranexamic acid administration in primary total hip arthroplasty: a randomized controlled trial. J Bone Joint Surg Am 2019; 101: 438-45.
17. Schnettler T, Papillon N, Rees H. Use of a Tourniquet in total knee arthroplasty causes a paradoxical ıncrease in total blood loss. J Bone Joint Surg Am 2017; 99: 1331-6.
18. Saad BN, Menken LG, Elkattaway S, Liporace FA, Yoon RS. Tranexamic acid lowers transfusion requirements and hospital length of stay following revision total hip or knee arthroplasty. Patient Saf Surg 2021; 15: 21.
19. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 2012; 344: e3054.
20. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Ann Intern Med 2011; 155: 39-51.

Original Article

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The effect of pandemic and COVID-19 vaccination campaigns on influenza and pneumococcal vaccination trends in patients with chronic diseases

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ABSTRACT

Aim: We planned this study to examine whether the measures taken against COVID-19 infection during the pandemic and COVID-19 vaccination process raise awareness about influenza and pneumococcal vaccines for patients in the risk group.

Material and Method: Patients over the age of 18 who were in the risk group according to CDC and had chronic diseases requiring influenza and pneumococcal vaccination were included in the study. A questionnaire consisting of seven questions was applied to all volunteers, showing their clinical demographic findings, their vaccination history, and whether the pandemic and COVID-19 vaccination processes contributed to the vaccination processes.

Results: It was found that 42.5% of the entire population had had a preventive vaccine before. With the COVID-19 pandemic, it was determined by the survey that 74.7% of the people would get their preventive vaccinations regularly from now on. After that, it was determined that the pandemic and COVID-19 vaccination processes were effective at a rate of 57.9% in the formation of this idea in the group that wanted to get a preventive vaccine.

Conclusion: As a result, the idea of having a preventive vaccination compared to the period before the pandemic increased during the pandemic period in relation to the events experienced in the pandemic. In this, it was determined that catching COVID-19 infection, hospitalization and intensive care unit admission and COVID-19 vaccination campaigns were effective in the cases in the risk group.

Keywords: Chronic kidney disease, diabetes, hearth disease, influenza, pneumococci, vaccine

INTRODUCTION

Mortality due to influenza and pneumococcal infections in patients with chronic diseases, advanced age and immunosuppressive status has a serious rate all over the World (1-4). According to data from the Center of Disease Control (CDC), 70% to 85% of deaths related to seasonal flu in recent years have occurred in people aged 65 and over. It has also been estimated that 50-70% of seasonal flu-related hospitalizations occur in people with this condition (5,6). Similarly, patients with chronic diseases such as asthma, chronic heart disease, chronic renal failure, chronic obstructive pulmonary disease and diabetes are at risk for both serious hospitalization and mortality in influenza infection (6). Likewise, according to CDC data, 1.5 million people in the United States were diagnosed with pneumonia in 2018, and 44,000 of them died. The majority of those who died were adults and people with chronic diseases (7).

When the data in the world is examined, although the mortality rate is seriously high in people with advanced age and chronic diseases, in cases of catching influenza and pneumococcal infections (8,9), the desired level in terms of preventive measures has not been reached all over the world. When the health policies of all developed countries are examined, influenza and pneumococcal vaccines are recommended for people at risk (10). However, awareness of both health professionals and people in the risk group is still insufficient.

The precautions taken all over the world during the COVID -19 pandemic, the warnings made to people in the risk group, and the vaccination studies against the COVID -19 infection created serious awareness for all humanity in terms of protection against COVID -19 infection (11). This situation created the feeling that precautions should be taken against other infections (pneumococcal, influenza, etc.) for people in the risk group.

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In this study, we planned this study to examine whether the measures taken against COVID -19 infection during the pandemic and COVID -19 vaccination process raise awareness about influenza and pneumococcal vaccines for patients in the risk group.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 27.10.2021, Decision No: E2-21-970). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study design

Patients over the age of 18 who were in the risk group according to CDC (6) and had chronic diseases requiring influenza and pneumococcal vaccination were included in the study. A questionnaire consisting of seven questions was applied to all volunteers, showing their clinical demographic findings, their vaccination history, and whether the pandemic and COVID -19 vaccination processes contributed to the vaccination processes **Figure 1.**

In our study, influenza and pneumococcal vaccines were classified as protective –preventive vaccines.

Statistical Analysis

Statistical analyses of collected data were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Determination of the normally distributed data was conducted using the Kolmogorov-Smirnov test. Numerical variables that had normal distribution were expressed as the mean ± standard deviation, while those with non-normal distribution were expressed as the median (min-max). Categorical variables were expressed as numbers and percentages. Student's t-test or the Mann-Whitney U test was used to compare numerical variables between the groups. Chi-square, Yates's correction, and Fisher exact chi-square tests were used for comparisons of categorical data. $P < 0.05$ was taken as statistical significance.

RESULTS

The clinical and demographic findings of the study population are summarized in **Table 1**. A total of 513 volunteers were included in the study. It was determined that 295 (%57.5) of them did not have a preventive vaccine before, and 218 (%42.5) of them were previously vaccinated. It was observed that 214 (41.7%) people in the entire population were previously infected with COVID -19. It was determined that 135 (45.8%) of them were in the group that did not have a preventive vaccine before, and 79 (36.2%) were in the group that had a preventive vaccine before.

THE EFFECT OF THE PANDEMIC PROCESS AND COVID-19 VACCINE CAMPAIGNS ON THE PROPHYLACTIC VACCINATION TENDENCY

Name-Surname: **Age:**

Gender: A. Female B. Male

Education status: A. Illiterate B. Primary education C. High school D. University

1- Have you had a Covid-19 infection?

A. Yes **B.** No

□ If your answer is "YES"; did you need hospitalization in follow-up?

A. Yes **B.** No

□ If your answer is "YES"; did you need intensive care stay in hospital follow-up?

A. Yes **B.** No

2 – Have you had the Covid-19 vaccine?

A. Yes **B.** No

3- Chronic disease status

	Yes	No
Chronic disease		
Diabetes		
Chronic Heart Disease		
Chronic Kidney Disease		
Chronic Lung Disease		
Chronic Liver Disease		
Sickle Cell Anemia / Hemoglobinemiapathy		
Immunosuppressed Condition		
splenectomy		
Other :		

3- Do you know that in cases of chronic disease such as diabetes, chronic heart disease, chronic kidney disease, chronic lung disease, chronic liver disease, nephrotic syndrome, sickle cell anemia, immunosuppression, spleen surgery, you should get a preventive vaccination against influenza infection once a year and against pneumonia every 5 years?

A. Yes **B.** No

If the answer is "NO", suggest prophylactic vaccination and proceed to question 6.

4- Have you ever had a preventive flu vaccine before?

A. Yes **B.** No

5- Have you ever had a preventive pneumonia vaccine?

A. Yes **B.** No

6- Do you plan to have a preventive flu vaccine in your next follow-up periods?

A. Yes **B.** No

7- Are you considering getting a pneumonia vaccine in your next follow-up periods?

A. Yes **B.** No

□ If your answer is "YES"; What made you want to be vaccinated?

(You can tick more than one option)

☐	Have had a previous preventive flu/pneumonia vaccine
☐	Physician information
☐	Having a Covid-19 Infection
☐	The need for follow-up in the inpatient service during the Covid-19 Infection process
☐	The need for follow-up in the intensive care unit during the Covid-19 Infection
☐	Vaccination campaigns during the pandemic
☐	Being vaccinated against Covid-19
☐	Other :

Figure 1. Prophylactic vaccine questionnaire

The rate of those who had the COVID -19 vaccine was higher in the group who had a preventive vaccine before compared to did not (93.6% vs 87.5%, p=0.025). While the rate of preventive vaccination in the whole population was 42.5%, after that, the thought of having a preventive vaccination increased to 74.7%. Proportion of those who thought that would get their preventive vaccinations regularly from now on was higher in the group who had a preventive vaccine before compared to did not (83.9% vs 67.8%, $p < 0.001$). Factors in wanting to have their preventive vaccinations regularly from now on: 26.7% of them having a preventive vaccination before, 67.3% based on the physician's information, 13.9% of having COVID-19 infection, 8% of hospitalizations due to

COVID-19 infection, hospitalization to intensive care due to COVID-19 infection % 2.1, raising awareness of current COVID-19 vaccination campaigns 11.3% and getting COVID-19 vaccine 8.4% (**Table 1**).

In the whole population, it was determined that the vaccination campaigns against COVID-19 infection and the COVID-19 pandemic were effective at a rate of 43.3% in making preventive vaccinations after that.

After this stage, the clinical and demographic findings of the volunteers who wanted and did not want to have a preventive vaccine are shown in **Table 2**. When we look at those who want to have a preventive vaccine, 35.8% of them have had a preventive vaccine before, while 90.1% of them have been found to be effective in informing the physician. With this having had COVID-19 infection in 18%, hospitalization due to COVID-19 infection in 10.7%, intensive care unit hospitalization due to COVID-19 infection in 2.9%, COVID-19 vaccine campaigns in 15.1% and had the COVID-19 vaccine in 11.2% was effective.

After that, it was determined that the pandemic and COVID-19 vaccination processes were effective at a rate of 57.9% in the formation of this idea in the group that wanted to get a preventive vaccine.

Table 1. Comparison of patients with and without a history of prophylactic vaccination

Variable	All population n=513	History of preventive vaccination		p
		No n=295	Yes n=218	
Gender, n (%)				0.853
Female	313 (61.0)	181 (61.4)	132 (60.6)	
Male	200 (39.0)	114 (38.6)	86 (39.4)	
Age, year	59.0±14.2	58.8±13.7	59.2±14.8	0.711
Education status, n (%)				0.294
Illiterate	48 (9.4)	31 (10.5)	17 (7.8)	
Primary school	254 (49.5)	151 (51.2)	103 (47.2)	
High school	111 (21.6)	63 (21.4)	48 (22.0)	
University	100 (19.5)	50 (16.9)	50 (22.9)	
History of Covid – 19, n (%)	214 (41.7)	135 (45.8)	79 (36.2)	0.031*
Hospitalization due to Covid – 9, n (%)	109 (21.2)	64 (21.7)	45 (20.6)	0.773
ICU hospitalization due to Covid – 19, n (%)	29 (5.7)	18 (6.1)	11 (5.0)	0.701
COVID-19 vaccine history, n (%)				0.025*
No	51 (9.9)	37 (12.5)	14 (6.4)	
Yes	462 (90.1)	258 (87.5)	204 (93.6)	
Comorbidity, n (%)				
Diabetes	333 (64.9)	194 (65.8)	139 (63.8)	0.639
COPD	62 (12.1)	30 (10.2)	32 (14.7)	0.121
Heart disease	178 (34.7)	107 (36.3)	71 (32.6)	0.384
Chronic kidney disease	45 (8.8)	25 (8.5)	20 (9.2)	0.875
Chronic liver disease	16 (3.1)	9 (3.1)	7 (3.2)	0.999
Immunodeficiency	33 (6.4)	19 (6.4)	14 (6.4)	0.999
Splenectomy	3 (0.6)	2 (0.7)	1 (0.5)	0.999
History of preventive vaccination, n (%)				
No	295 (57.5)	295 (100.0)	-	
Yes	218 (42.5)	-	218 (100.0)	
Influenza vaccine	201 (39.2)	-	201 (92.2)	-
Pneumococcal vaccine	91 (17.7)	-	91 (41.7)	-
Consideration of preventive vaccination, n (%)				<0.001*
No	130 (25.3)	95 (32.2)	35 (16.1)	
Yes	383 (74.7)	200 (67.8)	183 (83.9)	
Factors in getting a preventive vaccine, n (%)				<0.001*
Have been vaccinated before	137 (26.7)	15 (5.1)	122 (56.0)	
Physician information	345 (67.3)	189 (64.1)	156 (71.6)	0.074
Having had Covid	69 (13.5)	39 (13.2)	30 (13.8)	0.859
Hospitalization due to Covid	41 (8.0)	24 (8.1)	17 (7.8)	0.999
ICU hospitalization due to covid	11 (2.1)	6 (2.0)	5 (2.3)	0.999
Covid vaccine campaigns	58 (11.3)	41 (13.9)	17 (7.8)	0.034*
Have had the Covid vaccine	43 (8.4)	23 (7.8)	20 (9.2)	0.630

Numerical variables were presented as mean±standard deviation or median (min-max), and categorical variables as numbers (%). *P<0.05 indicates statistical significance.
Abbreviations: ICU: Intensive Care Unit, COPD: Chronic Obstructive pulmonary Disease

Table 2. Comparison of patients considering and not considering preventive vaccination

Variable	The idea of getting a preventive vaccine.		p
	No n=130	Yes n=383	
Gender, n (%)			0.330
Female	84 (64.6)	229 (59.8)	
Male	46 (35.4)	154 (40.2)	
Age, year	53.4±15.0	60.8±13.4	<0.001*
Education status, n (%)			0.065
Illiterate	13 (10.0)	35 (9.1)	
Primary school	52 (40.0)	202 (52.7)	
High school	32 (24.6)	79 (20.6)	
University	33 (25.4)	67 (17.5)	
History of Covid – 19, n (%)	42 (32.3)	172 (44.9)	0.012*
Hospitalization due to Covid – 9, n (%)	11 (8.5)	98 (25.6)	<0.001*
ICU hospitalization due to Covid – 19, n (%)	2 (1.5)	27 (7.0)	0.015*
COVID-19 vaccine history, n (%)			0.001*
No	23 (17.7)	28 (7.3)	
Yes	107 (82.3)	355 (92.7)	
Comorbidity, n (%)			
Diabetes	70 (53.8)	263 (68.7)	0.002*
COPD	15 (11.5)	47 (12.3)	0.878
Heart disease	43 (33.1)	135 (35.2)	0.653
Chronic kidney disease	9 (6.9)	36 (9.4)	0.475
Chronic liver disease	5 (3.8)	11 (2.9)	0.795
Immunodeficiency	8 (6.2)	25 (6.5)	0.999
Splenectomy	-	3 (0.8)	0.729
History of preventive vaccination, n (%)			<0.001*
No	95 (73.1)	200 (52.2)	
Yes	35 (26.9)	183 (47.8)	
Influenza vaccine	34 (26.2)	167 (43.6)	<0.001*
Pneumococcal vaccine	2 (1.5)	89 (23.2)	<0.001*
Factors in getting a preventive vaccine, n (%)			
Have been vaccinated before	-	137 (35.8)	-
Physician information	-	345 (90.1)	-
Having had Covid – 19	-	69 (18.0)	-
Hospitalization due to Covid – 19	-	41 (10.7)	-
ICU hospitalization due to covid – 19	-	11 (2.9)	-
Covid – 19 vaccine campaigns	-	58 (15.1)	-
Have had the Covid – 19 vaccine	-	43 (11.2)	-

Numerical variables were presented as mean±standard deviation or median (min-max), and categorical variables as numbers (%). *P<0.05 indicates statistical significance.
Abbreviations: ICU: Intensive Care Unit, COPD: Chronic Obstructive pulmonary Disease

DISCUSSION

In this study, we examined whether COVID-19 infection, hospitalization and intensive care unit admissions due to this, and vaccination campaigns carried out all over the world in this process, increased awareness of protective vaccines in patients in the risk group. In our study, it was found that 42.5% of the entire population had had a preventive vaccine before. With the COVID-19 pandemic, it was determined by the survey that 74.7% of the people would get their preventive vaccinations regularly from now on. After that, it was determined that the pandemic and COVID-19 vaccination processes were effective at a rate of 57.9% in the formation of this idea in the group that wanted to get a preventive vaccine.

Considering the data of the World Health Organization and CDC, influenza and pneumococcal infections in patients with chronic diseases seem to cause a serious increase in hospitalization, intensive care unit admission, mortality and health expenses compared to the normal population (12,13). While these infections can be overcome in healthy individuals, they can have a very severe course in people with chronic diseases, people over 65 years of age and those with immunodeficiency. Considering the health policies of developed countries, this issue is very important. In other words, influenza and pneumococcal vaccines are administered free of charge for those in the risk group (14-17). Despite this, the application rates of preventive vaccines such as influenza and pneumococcus are still not at the desired

level in patients in the risk group in the world (17). When we look at the results of our study, it was determined that only 42.5% of this population, which is in the risk group, made their preventive vaccinations.

There are many factors responsible for this situation. The worst thing is that when the studies in the literature are examined, it is seen that health professionals do not have enough awareness on this issue (18-21). However, there is still a serious opposition to vaccines in the world. In addition, the awareness level of patients on this issue is very low (22). Informing physicians about this issue, explaining to the patients that the vaccine is actually more beneficial than harming, and adequately explaining to the patients that chronic diseases will progress and result in mortality in case of infection will eliminate these problems and enable us to reach an adequate level of preventive vaccination. In the study of Altay et al., it was revealed that pneumococcal, influenza and hepatitis vaccination rates increased after education (21). As a matter of fact, in our study, we found that informing a physician was effective in 90.1% of those considering preventive vaccination. Along with these, we observe that the knowledge of both physicians and patients about infection and vaccinations has increased significantly with the COVID-19 pandemic that has been going on for about 2 years recently. Because in all media and social life, pandemic, job loss due to pandemic, hospitalization and death rates in case of infection, kept up to date every day. This constantly warned the population in the risk group to protect themselves against infection. And it was also dominated by everyone that the idea of vaccination was the biggest factor in preventing infection, reducing hospitalization and mortality. This has also led to increased awareness of protection from other infections. We see this in the results of our study.

While the rate of getting the preventive vaccinations before the pandemic was 42.5%, the idea of taking the preventive vaccination after the pandemic increased to 74.7%. And we see that the COVID-19 pandemic is clearly effective in increasing this rate. In some of these cases in the risk group, COVID-19 infection and hospitalization due to this were effective, while in others, we see that the covid-19 vaccination campaigns were effective.

The main limitation of our study is that it was cross-sectional and only the thoughts of getting the preventive vaccinations of the cases were evaluated. Evaluation of the rate of vaccination of the cases in the follow-up removes this limitation.

As a result, the idea of having a preventive vaccination compared to the period before the pandemic increased during the pandemic period in relation to the events experienced in the pandemic. In this, it was determined that catching COVID-19 infection, hospitalization and intensive care unit admission and COVID-19 vaccination campaigns were effective in the cases in the risk group..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 27.10.2021, Decision No: E2-21-970).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. Lancet Infect Dis 2009; 9: 493-504.
2. Boey L, Bosmans E, Ferreira LB, et al. Vaccination coverage of recommended vaccines and determinants of vaccination in at-risk groups. Human Vaccines & Immunotherapeutics 2020; 16: 2136-43.
3. Doherty M, Schmidt-Ott R, Santos JI, et al. Vaccination of special populations: protecting the vulnerable. Vaccine 2016; 34: 6681-90.
4. Sarda C, Palma P, Rello J. Severe influenza: overview in critically ill patients. Curr Opin Crit Care 2019; 25: 449-57.
5. Sanz-Rojo S, Jiménez-García R, López-de-Andrés A, de Miguel-Diez J, Perez-Farinos N, Zamorano-León JJ. Influenza vaccination uptake among high-risk target groups and health care workers in Spain and change from 2017 to 2020. Vaccine 2021; 39: 7012-20.
6. Centers for Disease Control and Prevention. https://www.cdc.gov/flu/highrisk/index.htm. Access date: 23.01.2022.
7. Centers for Disease Control and Prevention. https://www.cdc.gov/pneumonia/prevention.html. Access date: 23.01.2022.
8. Tan L, Theilacker C. 12 Direct and indirect benefits of to vaccinating adults with influenza and pneumococcal vaccines, especially in patients with chronic diseases. Adult Vaccinations: Changing the Immunization Paradigm 2019: 69.
9. Hespanhol V, Bárbara C. Pneumonia mortality, comorbidities matter? Pulmonology 2020;26:123-9.
10. Okoli GN, Lam OL, Racovitan F, et al. Seasonal influenza vaccination in older people: A systematic review and meta-analysis of the determining factors. PLoS One 2020; 15: e0234702.
11. Dinleyici EC, Borrow R, Safadi MAP, van Damme P, Munoz FM. Vaccines and routine immunization strategies during the COVID-19 pandemic. Human Vaccines & Immunotherapeutics 2021; 17: 400-7.
12. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). Access date: 23.01.2022.

13. World Health Organization. https://www.who.int/health-topics/pneumonia#tab=tab_1. Access date: 23.01.2022.
14. Luyten J, Beutels P. The social value of vaccination programs: beyond cost-effectiveness. Health Affairs 2016; 35: 212-8.
15. Giese C, Mereckiene J, Danis K, O'Donnell J, O'Flanagan D, Cotter S. Low vaccination coverage for seasonal influenza and pneumococcal disease among adults at-risk and health care workers in Ireland, 2013: The key role of GPs in recommending vaccination. Vaccine 2016; 34: 3657-62.
16. Nichol KL, Zimmerman R. Generalist and subspecialist physicians' knowledge, attitudes, and practices regarding influenza and pneumococcal vaccinations for elderly and other high-risk patients: a nationwide survey. Archives of Internal Medicine 2001; 161: 2702-8.
17. Nagata JM, Hernández-Ramos I, Kurup AS, Albrecht D, Vivas-Torrealba C, Franco-Paredes C. Social determinants of health and seasonal influenza vaccination in adults≥ 65 years: a systematic review of qualitative and quantitative data. BMC Public Health 2013; 13: 1-25.
18. Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA 1999; 281: 908-13.
19. Nichol KL, Mac Donald R, Hauge M. Factors associated with influenza and pneumococcal vaccination behavior among high-risk adults. J General Int Med 1996; 11: 673-7.
20. Çiftci F, Şen E, Demir N, Çiftci O, Erol S, Kayacan O. Beliefs, attitudes, and activities of healthcare personnel about influenza and pneumococcal vaccines. Human Vaccines & Immunotherapeutics 2018; 14: 111-7.
21. Altay M, Ateş İ, Altay FA, Kaplan M, Akça Ö, Özkara A. Does education effect the rates of prophylactic vaccination in elderly diabetics? Diabetes Research and Clinical Practice 2016; 120: 117-23.
22. Stancu MA, Barratt J, Anaya MB. A Canadian perspective on pneumonia vaccination among at-risk groups: Increasing relevance in a pandemic era. Expert Meeting Report 2020.

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Severity of subchondral insufficiency knee fracture: is it associated with increasing age, femorotibial angle, and severity of meniscus extrusion?

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ABSTRACT

Aim: To evaluate the relationship between severity of subchondral insufficiency fracture of the knee (SIFK) and age, gender, knee alingment, meniscus tear, type and location, severity of meniscus extrusion, and degree of knee osteoarthritis.

Material and Method: This retrospective study included 308 patients with SIFK seen on MRI. SIFK lesions were categorized as grade 1 to 4, with distinction between low grade (1 and 2) and high grade (3 and 4). The relationships between SIFK grade and patients' age, body mass index (BMI), femorotibial angle (FTA), meniscus tear,type and location meniscusextrusiongrade and osteoarthritis (grade 0 to grade 4) evaluated.

Results: According to the gender, 39.3% were men and 60.7% were women. The distrubutin of the SIFK grades were respectively 42.2% grade 1, 30.8% grade 2, 22.7% grade 3 and 4.2% grade 4. FTAwas positively correlated with SIFK grade (from grade 1 to grade 4, respectively; 4.42±2.57, 5.09±2.26, 5.74±2.78 and 5.95±2.54) (p=0.002). No statistically significant difference was observed between height, weight and BMI and the degree of SIFK.The mean FTA was 4.99±2.57° in SIFK. The FTA angles showed a stastistically significance between low (4.73±2.48°) and high (5.71±2.69°)grade SIFK (p:0.003). Roc analysis showed that the FTA above 3.1° and the age above 52 year old were at risk. The mean extent of meniscal extrusion was larger in high grade SIFK (p=0.001). Multivariable logistic regression analysis showed that compared with low grade SIFK, high grade SIFK was more closely associated with age, FTA, lateral meniscus extrusion and medial meniscus tear type.

Conclusion: High-grade SIFK lesions are associated with higher FTA and older age. In particular, patients with acute knee pain, older than 52 years of ageanda higher FTA than 3.1°, we recommend to perform knee MRI if possible.

Keywords: SIFK, subchondral insufficiency fracture, meniscus extrusion, osteoarthritis

INTRODUCTION

Subchondral insufficiency fracture of the knee (SIFK) is a type of stress fracture that results in recurrent physiological or excessive stress-related micro-fractures in the subchondral bone of the knee joint (1). The SIFK lesion localizes at epiphysis of the knee joint (2). In SIFK lesion, patients usually present with knee pain with an acute onset and clinically lasting for several months, usually without trauma or with only minor trauma.

SIFK was first described by Ahlbäck et al. he named it "spontaneous osteonecrosis of the knee (SONK)" in 1968 (3). Yamamoto et al. (4) reported that the true nature of SONK is a subchondral fracture. If the subchondral fracture does not heal and eventually transforms into osteonecrosis, as a result osteochondral collapse occurs (4-7).

Although the pathological mechanism has not been fully elucidated, it has been suggested that intramedullary edema-like bone marrow signal intensity associated with subchondral microfractures, increased intraosseous pressure and decreased local blood circulation may play a role in the development of osteonecrosis (8). It is now widely accepted that SONK is the final stage of subchondral fracture and is part of the advanced stage of the SIFK spectrum (1).

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Fracture line and early-stage lesions in SIFK are often unclear on radiographs. As the lesion progresses, radiographic abnormalities become visible, including osteochondral defects or deformities of the epiphyses (9,10). In 1979 Koshino et al. proposed a clinical classification system for SONK based on symptoms and radiographic findings (11). The Koshino classification is still often used as a reference to determine treatment strategies. In 2019, Seyyid et al. (12) proposed a grading system based on MRI. A hypointense line on T2 sections in the affected condyle-subchondral region, diffuse bone marrow edema-like signal intensity, is the characteristic finding on MRI for the diagnosis of SIFK (12). The etiology of SIFK is considered to be multifactorial (1). Various risk factors and associated findings for SIFK have been reported to date (1). Excessive contact stress due to cartilage and meniscal injury plays an important role in the development of SIFK (1). The aim of the study was to evaluate the relationship between severity ofSIFKand age, gender, knee alingment, meniscus tear/ type/location, severity of meniscus extrusion, and degree of knee osteoarthritis.

MATERIAL AND METHOD

The study was carried out with the permission of Tokat Gaziosmanpaşa University Hospital Ethics Committee (Date: 2022, Decision No: 22-KAEK-019). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study performed at Tokat Gaziosmanpasa Universty. From January 2011 to December 2020 in our hospital, MRI data including the knee region for any reason were analyzed using the electronic patient record system. The picture archiving and communication system (PACS) program was used for all reconstructions and measurements (Sectra Workstation IDS7, Version 21.2.11.6289, ©2019 Sectra AB).

The available knee MRIs in the PACS system were screened for SIFK. The patients included in the study were those who were unanimously diagnosed with SIFK on MRI by two orthopedic physicians with at least 10 years of experience. The age,weight,height, body mass index (BMI) were recorded. The exclusion criteria were the patients with MRI images taken after an acute event associated with high-energy trauma, fracture or high-grade contusion, patients who did not have MRI images of a quality that could evaluate SIFK, patients who underwent surgical intervention such as meniscectomy in the knee, patients with infection in the knee region or patients with tumors were excluded from the study.

As described in previous studies, the SIFK evaluated using T2-fat suppression MRI based on MRI findings (12). In this study, a previously proposed MRI grading system for SIFK was used to help identify factors that may be associated with high-grade (HG) and low-grade (LG) SIFK (12) (**Figure 1**). The exact place of the SIFK lesion was classified as coronal (medial, central, lateral) and sagittal (anterior, middle, posterior).

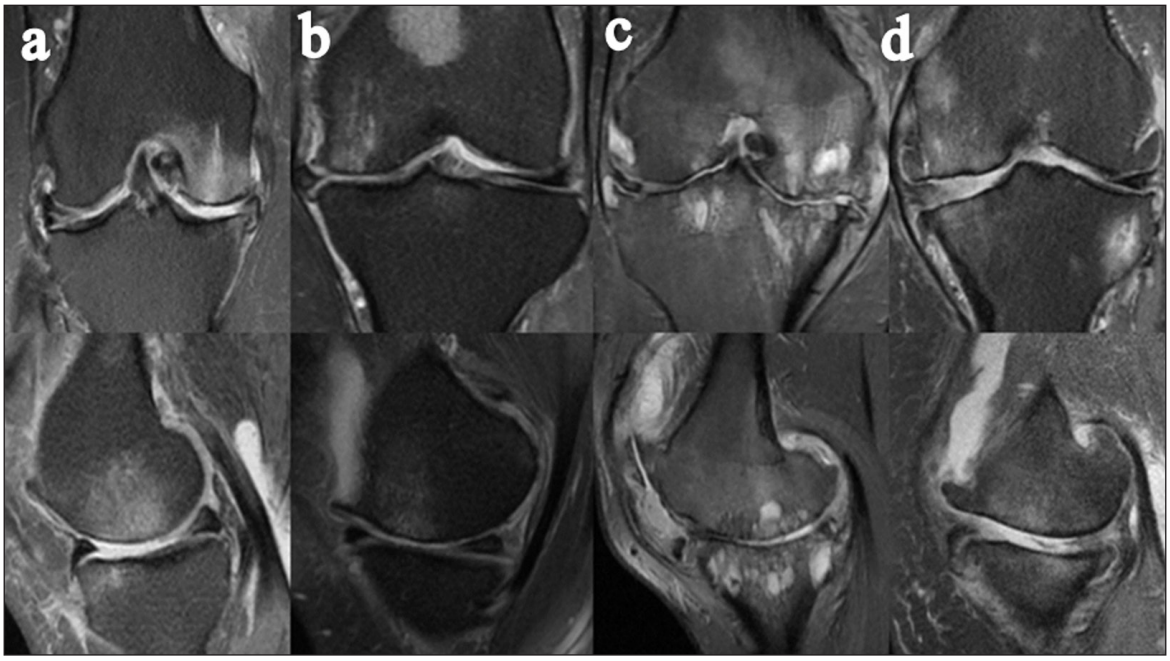

Figure 1: Sıfk grading; a) Grade 1: In MRI, there is a change in bone marrow signals like edema and there is no obvious fracture line. b) Grade 2: Subchondral fracture. c) Grade 3: Subchondral fracture with cystic changes. d) Grade 4: Subchondral collapse accompanied by subchondral fracture

Extruded or unextruded meniscal tears (medial or lateral) were detected on coronal fat-suppressed T2-weighted sequences. Meniscal tears and extrusions were classified as none, mild (<3 mm), moderate (3–5 mm), or severe (>5 mm) (13-15). Meniscal tears (medial or lateral) with or without extrusions were identified on the coronal and fat suppressed T2-weighted sequences. Also MRIs were scanned for additional medial and lateral meniscal tear to the knee accompanying meniscus root injury. The type of tear was recorded.

A mid-coronal plane was used to assess meniscus extrusion (16,17). The middle coronal plane, the section with the most prominent medial tibial eminence or the section with the maximum width of the tibial plateau were selected (16,17) (**Figure 2**). Osteoarthritis (OA) grade was described in the medial and lateral knee compartments. Medial and lateral knee compartments OA were classified according to The International Cartilage Repair Society (ICRS) MRI-based grading system (18). The degree of OA was defined separately in the medial and lateral knee compartments. The MRI-based The International Cartilage Repair Society (ICRS) grading system was used to classify the degree of OA (18).

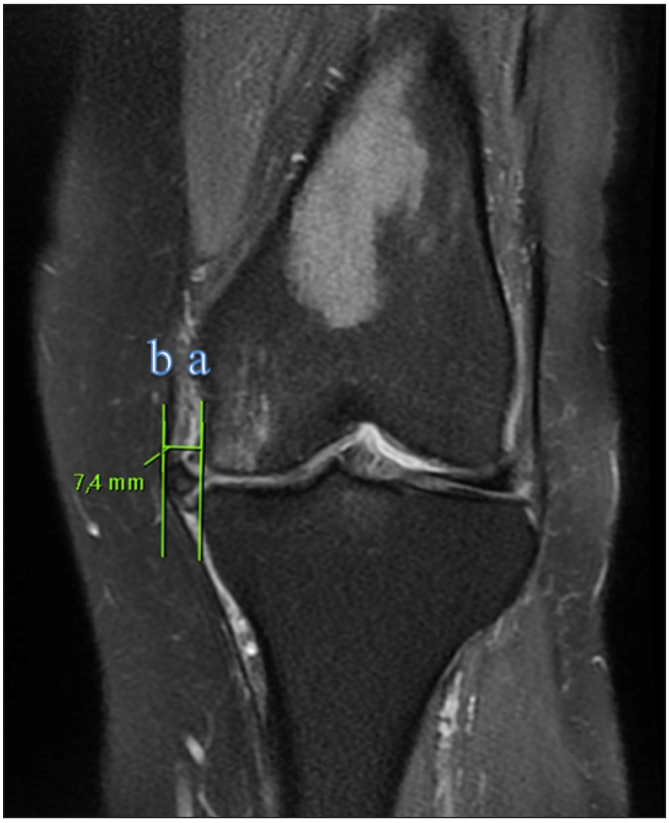

Figure 2: Measurement of medial meniscal extrusion. Extrusion is determined by measuring the distance in mm between the two perpendicular lines in the image showing the femoral medial condyle. First, a proper slice is selected in the coronal plane magnetic resonance imaging. Second, the exclusion of osteophytes are performed. Third, a perpendicular line (a) is drawn at a point at which the medial tibial plateau transitions from horizontal to vertical, then another perpendicular line (b) is drawn intersecting the outermost edge of the medial meniscus. The distance between the lines (a) and (b) is measured.

To avoid additional doses of radiation to patients, the FTA was measured using MRI images. The FTA was measured according to the method described by Iranpour-Boroujeni et al. (19). First, the mid-coronal axis is found. Second, a line connecting the condyles is drawn. Third, a line is drawn perpendicular to the line joining the condyles and the midpoint of these perpendiculars is found. Then, the alignment angle which is a negative number for valgus is calculated (**Figure 3**) (19).

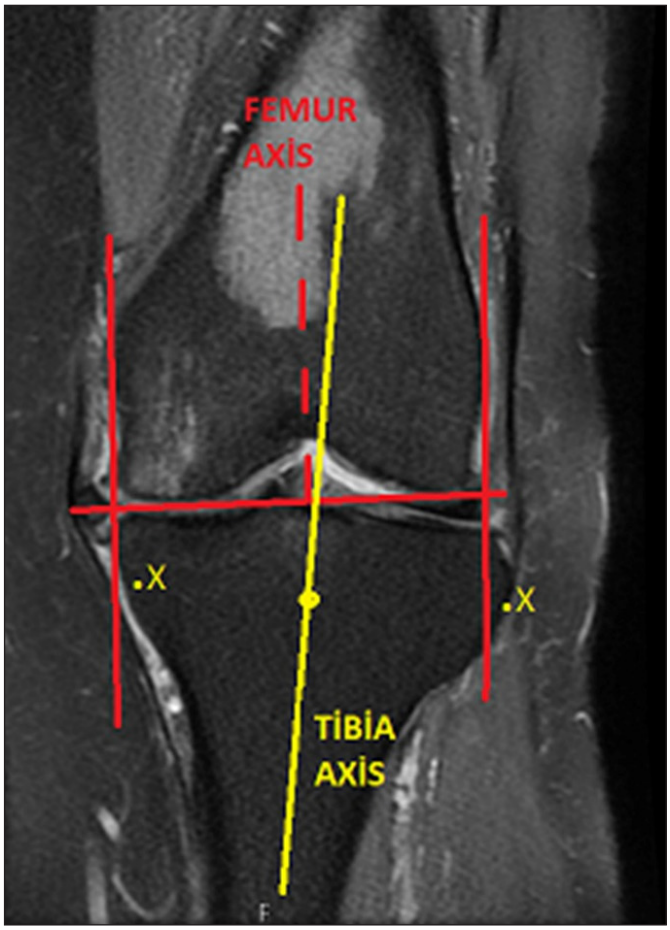

Figure 3: Determination of the femur tibial angle by the method proposed by Iranpour-Boroujeni et al. In the method, first, the mid-coronal axis is found, second, a line connecting the condyles is drawn. Third, a line is drawn perpendicular to the line joining the condyles and the midpoint of these

Statistical Analysis

Data are expressed as mean±standard deviation or frequency and percent. Independent sample t test or one way analysis of variance were used to compare the continuous normal data between/among groups. Chi-Square test was used to compare the categorical data between/among groups. Categorical variables were presented as a count and percentage.Receiver operating characteristic (ROC) analysis was applied to determine the power of variables in predicting significant SIFK classification. A p-value <0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

RESULT

After applying the inclusion and exclusion criteria, SIFK was identified in a total of 308 patients on knee MR imaging.Low grade SIFC was found in 225 patients, while high grade SIFC was found in 83 patients.The majority of SIFK lesions are low grade (LG; 73.1%).The rate of women (60.7%) was higher in patients with SIFK. In MRI, SIFK was most common in the central region (C), that is, in the most load-bearing area of the knee, both in the coronal (63.6%) and sagittal planes (52.9%). Meniscal tear was more common in the medial (39.9%) compartment.Medial meniscus(MM) root tear was detected in 25% of the patients.Grade 1 arthrosis was seen in 43.8% in the lateral compartment and in 26.9% in the medial compartment. While the rate of Grade 3 MKOA was 34% in those with high-grade SIFK, the rate of Grade 1 MKOA was 30.2% in those with low-grade SIFK. The degree of arthrosis in the medial compartment increased as the SIFK degree increased (p<0.001).Demographic data are given in **Table 1**.

The mean age of the patients participating in the study was 57.2±12.2 years and the mean BMI was 26.34±2.45 kg/m² (**Table 2**). High grade SIFK patients were older than the other patients. MM extrusion and FTA were higher in high grade SIFK patients compared to other patients.The mean FTA was 4.99±2.57 degrees varus. This explained that OA is more common medially. FTA was higher in patients with high grade SIFK (5.71±2.69) (p=0.003). A similar BMI was found between LG and HG SIFK lesions (26.37±2.37, 26.23±2.72, respectively)(**Table 2**).

Low grade SIFK MM extrusion was 1.95±2.55 mm, while high grade SIFK MM extrusion was 3.16±2.73 mm (**Table 2**). MM extrusion degree increased as the SIFK degree increased (p<0.001).While there was no statistically significant difference between the SIFK groups in terms of height, weight and BMI, there was a difference between numerical variables such as age, FTA, and meniscus extrusion (**Figure 4**).

Table 2. Distribution of numericalvariablessuch as age, weight, BMI, femorotibialangle, meniscusextrusionaccordingtothe SIFK system

Variables	Total	SIFK gradingsystem		p
		Lowgrade Mean±SS	High grade Mean±SS	
Age yıl	57.26±12.22	55.76±12.76	61.34±9.54	<0.001
Weight cm	73.13±7.05	73.15±6.95	73.07±7.34	0.860
Height kilogram	1.67±0.04	1.67±0.04	1.67±0.04	0.561
BMI	26.34±2.45	26.35±2.36	26.3±2.69	0.663
FTA	4.99±2.57	4.73±2.48	5.71±2.69	0.003
Medial meniscus extrusion(mm)	2.27±2.65	1.95±2.55	3.16±2.73	<0.001
Lateral meniscus extrusion(mm)	1.14±2.22	1.04±2.29	1.42±2	0.183

Independent samples t test was used

Table 1. Distribution of demographicdataby SIFK system

Variables	Total	SIFK grading system		p
		Low grade n (%)	High grade n (%)	
Gender				0.140
Female	187 (60.7)	131 (58.2)	56 (67.5)	
Male	121 (39.3)	94 (41.8)	27 (32.5)	
Lateralization				0.229
Left	172 (55.8)	121 (53.8)	51 (61.4)	
Right	136 (44.2)	104 (46.2)	32 (38.6)	
Lateral compartman arthrosis (LKOA)				<0.001
None	63 (20.5)	43 (19.1)	20 (24.1)	
Grade 1	135 (43.8)	116 (51.6)	19 (22.9)	
Grade 2	63 (20.5)	36 (16)	27 (32.5)	
Grade 3	28 (9.1)	17 (7.6)	11 (13.3)	
Grade 4	19 (6.2)	13 (5.8)	6 (7.2)	
Medial compartman arthrosis (MKOA)				<0.001
None	47 (15.3)	37 (16.4)	10 (12)	
Grade 1	83 (26.9)	68 (30.2)	15 (18.1)	
Grade 2	81 (26.3)	64 (28.4)	17 (20.5)	
Grade 3	59 (19.2)	30 (13.3)	29 (34.9)	
Grade 4	38 (12.3)	26 (11.6)	12 (14.5)	
SIFK Location on coronal plane				0.021
(P)1	88 (28.6)	74 (32.9)	14 (16.9)	
(C)2	196 (63.6)	134 (59.6)	62 (74.7)	
(I)3	24 (7.8)	17 (7.6)	7 (8.4)	
SIFK Location on sagittal plane				0.724
(A)1	29 (9.4)	20 (8.9)	9 (10.8)	
(C)2	163 (52.9)	122 (54.2)	41 (49.4)	
(P)3	116 (37.7)	83 (36.9)	33 (39.8)	
Locationof meniscal tear compartment of knee				<0.001
None	76 (24.7)	70 (31.1)	6 (7.2)	
Medial	123 (39.9)	84 (37.3)	39 (47)	
Lateral	9 (2.9)	7 (3.1)	2 (2.4)	
Both	100 (32.5)	64 (28.4)	36 (43.4)	
Medialmeniscus tear type				<0.001
None	87 (28.2)	79 (35.1)	8 (9.6)	
Root	77 (25)	50 (22.2)	27 (32.5)	
Radial	27 (8.8)	13 (5.8)	14 (16.9)	
Other	117 (38)	83 (36.9)	34 (41)	
Lateralmeniscus tear type				0.038
None	198 (64.3)	154 (68.4)	44 (53)	
Root	3 (1)	2 (0.9)	1 (1.2)	
Vertical	1 (0.3)	0 (0)	1 (1.2)	
Other	106 (34.4)	69 (30.7)	37 (44.6)	
Medial meniscus extrusion group				0.001
None	144 (46.8)	118 (52.4)	26 (31.3)	
Mild	50 (16.2)	37 (16.4)	13 (15.7)	
Moderate	58 (18.8)	40 (17.8)	18 (21.7)	
Severe	56 (18.2)	30 (13.3)	26 (31.3)	
Lateral meniscus extrusion group				<0.001
None	228 (74)	179 (79.6)	49 (59)	
Mild	22 (7.1)	10 (4.4)	12 (14.5)	
Moderate	31 (10.1)	14 (6.2)	17 (20.5)	
Severe	27 (8.8)	22 (9.8)	5 (6)	

Pearson chi-square test was used.

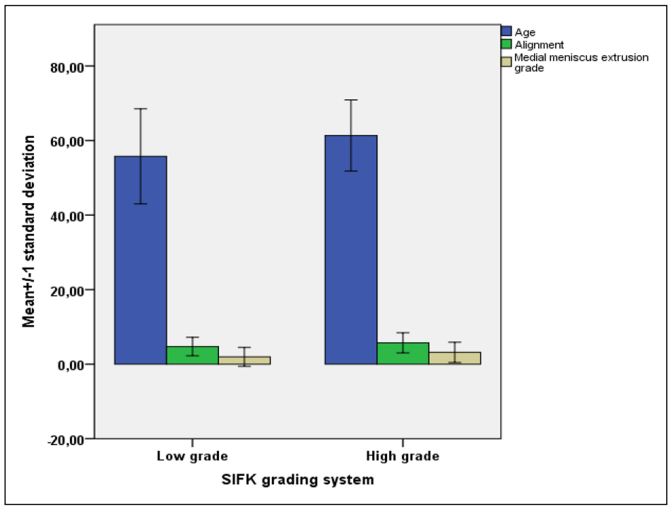

Figure 4: Figure bar graph with mean+/-1 standard deviaton of variables by SIFK grading system

While 16.9% of high-grade SIFKs were radial meniscus tears and 32.5% of them were meniscus root tears, this rate was lower in low-grade SIFKs. There was a significant difference between the SIFK groups in terms of MM extrusion (**Figure 5**). While there was no MM extrusion in 31.3% of high-grade SIFCs, this rate was higher in low-grade SIFKs (52.4%).

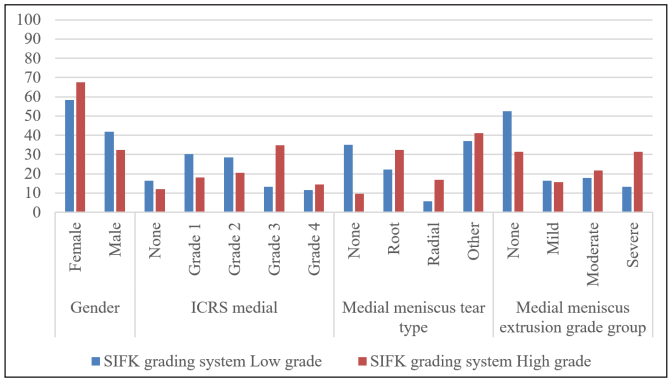

Figure 5: Accordingtothe SIFK grading system, age, medial compartment arthrosis, medial meniscus tear type, classification of medial meniscus extrusion

If we evaluate the Classification of SIFK, grade 1, grade 2, grade 3, grade 4 separately, there was a significant difference in terms of lateral compartment OA, medial compartment OA, SIFK location on coronal plane, location of meniscal tear compartment of knee, MM tear type, lateral meniscus (LM) tear type, MM extrusion grade and LM extrusion grade (**Table 3**). Among all SIFK groups, SIFK Grade 1 was the highest (42.2%) (**Table 3**).

The mean age of grade 4 SIFC was 61.5±5.01 years, and the mean age of grade 1 SIFC was 54.39±12.83 years. The ages of the patients were increasing from grade 1 to grade 4 ($p<0.001$). As the SIFK Degree increased, the FTA angle increased ($p=0.002$).The FTA was higher in grade 3-4 SIFK patients. As the grade increased, MM extrusion increased ($p<0.001$) (**Table 4**).

Table 3.Distribution of variables by classifcation of SIFK

Variables	Classifcation of SIFK				p
	Grade 1 n (%)	Grade2 n (%)	Grade3 n (%)	Grade4 n (%)	
Gender					0.337
Female	76 (58.5)	55 (57.9)	49 (70)	7 (53.8)	
Male	54 (41.5)	40 (42.1)	21 (30)	6 (46.2)	
Lateralization					0.553
Left	68 (52.3)	53 (55.8)	42 (60)	9 (69.2)	
Right	62 (47.7)	42 (44.2)	28 (40)	4 (30.8)	
LKOA					0.001
None	32 (24.6)	11 (11.6)	18 (25.7)	2 (15.4)	
Grade 1	63 (48.5)	52 (54.7)	18 (25.7)	2 (15.4)	
Grade 2	20 (15.4)	16 (16.8)	21 (30)	6 (46.2)	
Grade 3	6 (4.6)	11 (11.6)	8 (11.4)	3 (23.1)	
Grade 4	9 (6.9)	5 (5.3)	5 (7.1)	0 (0)	
MKOA					<0.001
None	28 (21.5)	9 (9.5)	10 (14.3)	0 (0)	
Grade 1	45 (34.6)	22 (23.2)	16 (22.9)	0 (0)	
Grade 2	28 (21.5)	36 (37.9)	14 (20)	3 (23.1)	
Grade 3	15 (11.5)	15 (15.8)	20 (28.6)	9 (69.2)	
Grade 4	14 (10.8)	13 (13.7)	10 (14.3)	1 (7.7)	
SIFK Location on coronalplane					0.025
(P)1	50 (38.5)	23 (24.2)	13 (18.6)	2 (15.4)	
(C)2	73 (56.2)	62 (65.3)	50 (71.4)	11 (84.6)	
(I)3	7 (5.4)	10 (10.5)	7 (10)	0 (0)	
SIFK Location on sagital plan					0.054
(A)1	10 (7.7)	10 (10.5)	6 (8.6)	3 (23.1)	
(C)2	81 (62.3)	40 (42.1)	37 (52.9)	5 (38.5)	
(P)3	39 (30)	45 (47.4)	27 (38.6)	5 (38.5)	
Location of menisca ltear compartment of knee					<0.001
None	54 (41.5)	16 (16.8)	6 (8.6)	0 (0)	
Medial	47 (36.2)	37 (38.9)	30 (42.9)	9 (69.2)	
Lateral	4 (3.1)	3 (3.2)	2 (2.9)	0 (0)	
Both	25 (19.2)	39 (41.1)	32 (45.7)	4 (30.8)	
Medial meniscus tear type					<0.001
None	59 (45.4)	20 (21.1)	8 (11.4)	0 (0)	
Root	22 (16.9)	28 (29.5)	17 (24.3)	10 (76.9)	
Radial	6 (4.6)	7 (7.4)	14 (20)	0 (0)	
Other	43 (33.1)	40 (42.1)	31 (44.3)	3 (23.1)	
Lateral meniscus tear type					0.011
None	101 (77.7)	53 (55.8)	36 (51.4)	8 (61.5)	
Root	1 (0.8)	1 (1.1)	1 (1.4)	0 (0)	
Vertical	0 (0)	0 (0)	1 (1.4)	0 (0)	
Other	28 (21.5)	41 (43.2)	32 (45.7)	5 (38.5)	
Medial meniscus extrusion grade					<0.001
None	73 (56.2)	45 (47.4)	23 (32.9)	3 (23.1)	
Mild	19 (14.6)	17 (17.9)	14 (20)	0 (0)	
Moderate	26 (20)	14 (14.7)	17 (24.3)	1 (7.7)	
Severe	12 (9.2)	19 (20)	16 (22.9)	9 (69.2)	
Lateral meniscus extrusion grade					<0.001
None	111 (85.4)	67 (70.5)	43 (61.4)	7 (53.8)	
Mild	6 (4.6)	4 (4.2)	9 (12.9)	3 (23.1)	
Moderate	8 (6.2)	7 (7.4)	15 (21.4)	1 (7.7)	
Severe	5 (3.8)	17 (17.9)	3 (4.3)	2 (15.4)	

Pearson chi-square test was used.

Table 4.Distribution of age, weight, BMI, femorotibialangle, meniscusextrusionaccordingtothe SIFK system.

Variables	Classifcation of SIFK				p
	Grade 1 Mean±SS	Grade 2 Mean±SS	Grade 3 Mean±SS	Grade 4 Mean±SS	
Age	54.39±12.83 (a)	58.02±11.85 (b)	61.75±10.33 (c)	61.5±5.01 (abc)	<0.001
Weight	73.77±6.73	72.38±7.16	72.76±7.66	74.23±5.8	0.446
Height	1.67±0.04	1.66±0.04	1.67±0.04	1.67±0.03	0.195
BMI	26.54±2.3	26.13±2.43	26.21±2.79	26.59±2.28	0.782
Femorotibial angle	4.42±2.57 (a)	5.09±2.26 (b)	5.74±2.78 (b)	5.95±2.54 (b)	0.002
Medial meniscus extrusion	1.73±2.37 (a)	2.29±2.79 (ab)	2.73±2.43 (b)	5.09±3.29 (c)	<0.001
Lateral meniscus extrusion	0.64±1.73 (a)	1.63±2.81 (b)	1.33±1.95 (b)	1.63±2.29 (ab)	0.006

One way ANOVA was used. (abc): In same row, Common letter sindicate statistical in significance.

Age 52 years and older with 88.7% sensitivity and 33% specificity (AUC 0.621; p <0.001), a FTA of 3.1 degrees or more, with 89.1% sensitivity and 31.5% specificity (AUC 0.605; p=0.003), MM extrusion greater than 2.5 mm can predict high-grade SIFK lesion, with a sensitivity of 59.04% and a specificity of 65.33% (AUC 0.633; p <0.001) (**Figure 6**).

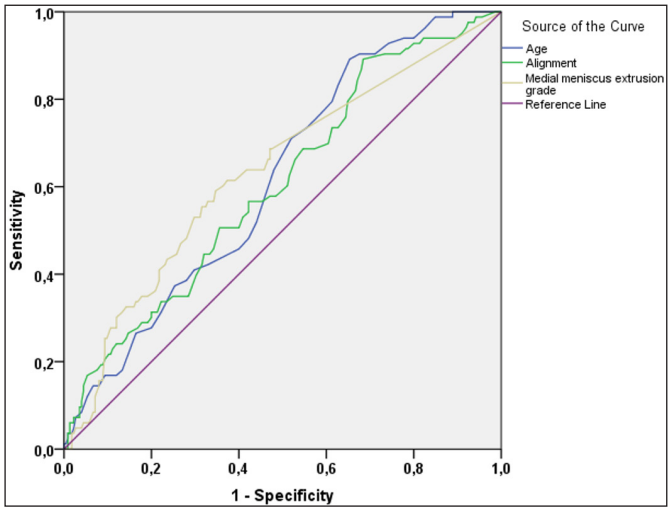

Figure 6: Age, meniscus extrusion and femorotibial angle ROC analysis graph showing its relationship with SIFK lesion

DISCUSSION

Current study showed in ROC analysis that three important risk factors,increasedMM extrusion, older age and increased FTA, contribute to the development of SIFK. FTA was affected by meniscus tear type and exturation. In particular, ≥52 years of age, with acute knee pain with FTA ≥3.1°, we recommend to perform MRI if possible. Our study found that the degree of OA in a joint was directly related to the severity of SIFK.

In the healthy population, the distal femur and proximal tibia orientation are usually parallel (20). Increased FTA causes excessive shear stress on the articular cartilage by increasing joint line obliquity. According to the study of Nakayama's et al. (21) shear stress in the medial compartment is increased by 1.5 times if the joint line is inclined five degrees from normal, and doubled if the joint line is inclined by 10°. Cooke et al. (22) found that the progression of OA was affected by increasing varus in the distal femur and/or proximal tibia. Tsukamoto et al. (23) suggested that two important risk factors, such as varus deformity in the proximal tibia and knee joint laxity, contribute to the development of the early phase of SONK. There are studies in the literature with opposite findings. For example Yamagami et al. (20) did nor find any significant difference for the mean tibial varus angle between SONK and OA.

Previous studies have revealed that tears of the posterior root of the MM are highly associated with SIFK and hypothesized that biomechanical changes secondary to loss of ring strength result in increased contact pressures and axial loading on weight-bearing surfaces (24). In our study, radial and root tear in the MM rate was 28% in patients with low grade while 57.9% in patients with high grade.

Several reports have shown an association between knee OA and SIFK (1,6,25). In our study, only 15,3% of the patients had no signs of OA in the medial compartment, while this rate was 20.5% in the lateral compartment. In our study group, the high number of patients with OA is not clearly known as it is a cross-sectional study and there is no follow-up, as it is a cross-sectional study and whether SIFK triggers OA or whether OA causes SIFK. Since the meniscus has the role of protecting the knee joint surface from mechanical stress, it is known that meniscus injury is also associated with the development of knee OA (26).

Most of these meniscal abnormalities are medial meniscal tears, often on the same side of the SIFK (25,27). The most common tear is the posterior root tear, followed by a radial tear in the posterior horn (27). If this ring mechanism is disrupted due to meniscal tears, extrusion or resections, the contact pressure on the knee's loading surface increases, which can lead to the development of SIFK (26). There are some reports showing a relationship between SIFK and medial meniscal tear or showing a relationship between SIFK and meniscectomy (7). Most of these meniscal abnormalities are medial meniscal

tears, often on the same side of the SIFK (25). The most common tear is the posterior root tear, followed by a radial tear in the posterior (5). Tears in the posterior root of the meniscus are considered a risk factor for meniscus extrusion (24), medial meniscal tear was higher with a rate of 39.9% in our study, but the rate of medial meniscus root and radial tear was relatively low in our study (13.9%). Medial meniscal tear has been suggested as a potential etiology of SONK (24). Disruption of collagen fibers in the meniscus causes meniscus extrusion, which causes a change in the load distribution in the knee (28). Loss of significant load distribution function with meniscal extrusion may simulate a situation similar to meniscectomy (7,29). Arthroscopic meniscectomy results in osteonecrosis of the knee in some patients (30). Greater meniscus extrusion results in greater opening and articular surface contact and greater force in the subchondral area. Our study shows that both medial and lateral meniscus extrusion is greater in cases with severe high grade SIFK. The rate of patients without MM extrusion was 52.4% in low-grade SIFK patients, while it was 31.3% in high-grade SIFK patients. However, not all SIFK occurs in the setting of a meniscal tear, and not all meniscal tears progress to SIFK. As a matter of fact, 24.7% of the patients in our study did not have any meniscal tear.

Plett et al. (25) reported that 64.4% (47/73) of 73 SIFK patients were women. In our study, this rate was 60.7%. It was previously described that SIFK is more common in female patients aged 60 years and over (31). In our study, the rate of women was high. In addition, the mean age of women was higher than that of men. In the literature, it has been reported that advanced lesions are more common in women (32). In our study, high grade SIFK was more common in women with 67.5%.

SIFK is most commonly seen in the weight-bearing region of the medial femoral condyle (MFC)(33). Wilmot et al analyzed 74 cases of SIFK and found that 64.9% (48/74) of the cases were in the medial femoral condyle, 16.2% (12/74) were in the lateral femoral and 2.7% (2/74) were at medial tibial condyles. The striking finding here was that the lesion was in the middle 1/3 of the condyle, which carries the load (70-77%) (32). In our study, in the sagittal plane the SIFK was in the coronal plane with a rate of 63.6% and 52.9% were in the central.

Studies on the relationship between patient weight and SIFK have shown that overweight patients have more stress on the lower extremity joints. Zanetti et al. found that 40.6% (13/32) of SIFK patients were overweight or obese (body mass index >25.0 kg/m^2) (34). However, it was recently reported that body weight was not associated with the prognosis of SIFK (12). In our study, no difference was found in terms of weight, height and BMI.

This study has several limitations. First, this study is a retrospective and cross-sectional analysis. It is not clear whether SIFK causes OA or, on the contrary, OA causes SIFK, since there is no clinical follow-up of the patients. There is no tracking of the FTA angle. We were unable to determine whether the increased FTA was the cause or the result. Prospective long-term studies are needed to clarify this point. We compared OA classification patients with MRI only. Standing knee X-rays and ortho-radiography were not available.

CONCLUSION

As a result, radiographic parameters of SIFK were compared. Significantly larger FTA deformity was observed in SIFK. Clinicians should suspect the onset of SIFK in patients with acute knee pain with an FTA greater than 3.1°.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University Hospital Ethics Committee (Date: 2022, Decision No: 22-KAEK-019).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Hussain ZB, Chahla J, Mandelbaum BR, Gomoll AH, LaPrade RF. The role of meniscal tears in spontaneous osteonecrosis of the knee: a systematic review of suspected etiology and a call to revisit nomenclature. Am J Sports Med 2019; 47: 501-7.
2. Pathria MN, Chung CB, Resnick DL. Acute and stress-related injuries of bone and cartilage: pertinent anatomy, basic biomechanics, and imaging perspective. Radiology 2016; 280: 21-38.
3. Ahlbäck S, Bauer GC, Bohne WH. Spontaneous osteonecrosis of the knee. Arthritis Rheumatism 1968; 11: 705-33.
4. Yamamoto T, Bullough PG. Spontaneous osteonecrosis of the knee: the result of subchondral insufficiency fracture. JBJS 2000; 82: 858.
5. Tanaka Y, Mima H, Yonetani Y, Shiozaki Y, Nakamura N, Horibe S. Histological evaluation of spontaneous osteonecrosis of the medial femoral condyle and short-term clinical results of osteochondral autografting: a case series. The Knee 2009; 16: 130-5.

6. Mears SC, McCarthy EF, Jones LC, Hungerford DS, Mont MA. Characterization and pathological characteristics of spontaneous osteonecrosis of the knee. The Iowa Orthopaedic J 2009; 29: 38.
7. Higuchi H, Kobayashi Y, Kobayashi A, Hatayama K, Kimura M. Histologic analysis of postmeniscectomy osteonecrosis. Am J Orthop 2013; 42: e2.
8. Madry H, van Dijk CN, Mueller-Gerbl M. The basic science of the subchondral bone. Knee Surgery Sports Traumatology Arthroscopy 2010; 18: 419-33.
9. Houpt JB, Pritzker KP, Alpert B, Greyson N, Gross AE, editors. Natural history of spontaneous osteonecrosis of the knee (SONK): a review. Seminars in Arthritis and Rheumatism; 1983: Elsevier.
10. Pape D, Seil R, Fritsch E, Rupp S, Kohn D. Prevalence of spontaneous osteonecrosis of the medial femoral condyle in elderly patients. Knee Surgery Sports Traumatology Arthroscopy 2002; 10: 233-40.
11. Koshino T, Okamoto R, Takamura K, Tsuchiya K. Arthroscopy in spontaneous osteonecrosis of the knee. The Orthopedic Clin North Am 1979; 10: 609-18.
12. Sayyid S, Younan Y, Sharma G, et al. Subchondral insufficiency fracture of the knee: grading, risk factors, and outcome. Skeletal Radiology 2019; 48: 1961-74.
13. Yasuda T, Ota S, Fujita S, Onishi E, Iwaki K, Yamamoto H. Association between medial meniscus extrusion and spontaneous osteonecrosis of the knee. Int J Rheumatic Dis 2018; 21: 2104-11.
14. Sung JH, Ha JK, Lee DW, Seo WY, Kim JG. Meniscal extrusion and spontaneous osteonecrosis with root tear of medial meniscus: comparison with horizontal tear. Arthroscopy J Arthroscopic Related Surg 2013; 29: 726-32.
15. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis and Cartilage 2011; 19: 990-1002.
16. Swamy N, Wadhwa V, Bajaj G, Chhabra A, Pandey T. Medial meniscal extrusion: detection, evaluation and clinical implications. Eur J Radiol 2018; 102: 115-24.
17. Bruns K, Svensson F, Turkiewicz A, et al. Meniscus body position and its change over four years in asymptomatic adults: a cohort study using data from the Osteoarthritis Initiative (OAI). BMC Musculoskeletal Disorders 2014; 15: 1-11.
18. Kohyama S, Ogawa T, Mamizuka N, Hara Y, Yamazaki M. A magnetic resonance imaging–based staging system for osteochondritis dissecans of the elbow: a validation study against the International Cartilage Repair Society classification. Orthopaedic J Sports Med 2018; 6: 2325967118794620.
19. Iranpour-Boroujeni T, Li J, Lynch J, Nevitt M, Duryea J, Investigators O. A new method to measure anatomic knee alignment for large studies of OA: data from the Osteoarthritis Initiative. Osteoarthritis and Cartilage 2014; 22: 1668-74.
20. Yamagami R, Taketomi S, Inui H, Tahara K, Tanaka S. The role of medial meniscus posterior root tear and proximal tibial morphology in the development of spontaneous osteonecrosis and osteoarthritis of the knee. The Knee 2017; 24: 390-5.
21. Nakayama H, Iseki T, Kanto R, Daimon T, Kashiwa K, Yoshiya S. Analysis of risk factors for poor prognosis in conservatively managed early-stage spontaneous osteonecrosis of the knee. The Knee 2016; 23: 25-8.
22. Cooke T, Sheehy L, Scudamore RA. What information must measures provide to demonstrate the problems in knee alignment and osteoarthritis? Osteoarthritis and Cartilage 2010; 18: 1544.
23. Tsukamoto H, Saito H, Saito K, et al. Radiographic deformities of the lower extremity in patients with spontaneous osteonecrosis of the knee. The Knee 2020; 27: 838-45.
24. Robertson D, Armfield D, Towers J, Irrgang J, Maloney W, Harner C. Meniscal root injury and spontaneous osteonecrosis of the knee: an observation. J Bone Joint Surg British 2009; 91: 190-5.
25. Plett SK, Hackney LA, Heilmeier U, et al. Femoral condyle insufficiency fractures: associated clinical and morphological findings and impact on outcome. Skeletal Radiology 2015; 44: 1785-94.
26. Hunter D, Zhang Y, Niu J, et al. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis Rheumatism 2006; 54: 795-801.
27. Yao L, Stanczak J, Boutin RD. Presumptive subarticular stress reactions of the knee: MRI detection and association with meniscal tear patterns. Skeletal Radiology 2004; 33: 260-4.
28. Bessette GC. The meniscus. Orthopedics 1992; 15: 35-42.
29. Gale D, Chaisson C, Totterman S, Schwartz R, Gale M, Felson D. Meniscal subluxation: association with osteoarthritis and joint space narrowing. Osteoarthritis and Cartilage 1999; 7: 526-32.
30. Brahme SK, Fox J, Ferkel R, Friedman M, Flannigan B, Resnick D. Osteonecrosis of the knee after arthroscopic surgery: diagnosis with MR imaging. Radiology 1991; 178: 851-3.
31. Aglietti P, Insall J, Buzzi R, Deschamps G. Idiopathic osteonecrosis of the knee. Aetiology, prognosis and treatment. J Bone Joint sSurg British 1983; 65: 588-97.
32. Wilmot AS, Ruutiainen AT, Bakhru PT, Schweitzer ME, Shabshin N. Subchondral insufficiency fracture of the knee: a recognizable associated soft tissue edema pattern and a similar distribution among men and women. Eur J Radiol 2016; 85: 2096-103.
33. al-Rowaih A, Björkengren A, Egund N, Lindstrand A, Wingstrand H, Thorngren K-G. Size of osteonecrosis of the knee. Clin Orthopaedics Related Research 1993: 68-75.
34. Zanetti M, Romero J, Dambacher M, Hodler J. Osteonecrosis diagnosed on MR images of the knee: relationship to reduced bone mineral density determined by high resolution peripheral quantitative CT. Acta Radiologica 2003; 44: 525-31.

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The relationship between malignancy and Behçet's disease features

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ABSTRACT

Introduction: Behçet's disease (BD) is an autoimmune, multisystemic vasculitis characterized by chronic inflammation. Autoimmune responses in BD could drive chronic inflammation which is a risk for malignant transformation. Some genetic, environmental, clinical features and immunosuppressive treatments in BD may increase the risk of malignancy. Common genetic factors and similar environmental factors play a role in the pathogenesis of some autoimmune diseases and malignancies. We hypothesized that the frequency of comorbidity and clinical features of BD may differ in BD patients with a family history of malignancy. So, we aimed to compare the demographic and clinical characteristics features of the BD patients with and without a family history of malignancy.

Material and Method: The BD patients who admitted the rheumatology outpatient clinic consecutively were included in the study. The demographic and clinical characteristics, comorbidities including malignancy in BD patients and malignancies in their family were questioned. The acute phase reactant elevation of at least two follow-ups was accepted as chronic inflammation.

Results: A total of 98 patients (57% male) were included. Mean age was 43.5±12.3 years. The frequency of comorbidity was 60% and malignant/premalignant lesions were seen in 5% of the patients. All lesions were solid organ related and all of them were in women. History of BD and malignancy in patients' families was found 28% and 38%, respectively. The patients with and without malignancy in their family were compared. Female gender and the frequency of erythema nodosum were higher in the patients with malignancy in their family. The other demographic and clinical characteristics, chronic persistent inflammation and medical treatments were statistically. not different

Conclusion: Frequency of malignancy in BD patients' family was evaluated and to the best of our knowledge, there was no literature data on this subject interestingly. The family history of malignancy in BD patients could be associated with clinical characteristics. Further prospective studies were needed to show the clinical effect of malignancy history in families.

Keywords: Behçet's disease, comorbidity, malignancy, family history

INTRODUCTION

Behçet's disease (BD) is a systemic vasculitis that may involve various organ systems. Its prevalence in Turkey is 240 per 100,000 population, and mostly seen in the Mediterranean region and the Far East (1). Although the pathogenesis of BD is not clear, it is thought to occur in individuals with a genetic predisposition under the influence of environmental factors. HLA-B51 allele, T lymphocyte-mediated immune dysfunction, neutrophilic inflammation, endothelial damage (NETosis) including MHC class I molecules are pathways that play a role in the pathogenesis.. Immunosuppressants are the mainstay treatment agents in BD (2,3).

BD has previously been associated with an increased risk of malignancy, both solid tumours and hematologic malignancies (4-9). Common environmental triggers, altered immune system, genetic factors and long-term use of immunosuppressants may be responsible for development of malignancy in BD (10-13). In addition to the role in BD pathogenesis, the HLA-B51 polymorphism has also been reported to be related with lymphoma, cervical carcinoma, papillary thyroid carcinoma (14-16). In BD long-term ongoing inflammation may cause comorbidities and mortality but whether it provokes malignancy development is yet to be clarified (4).

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Family history of a patient encompasses common genetic, behavioural, and environmental risk factors that can affect health among biological relatives. Likewise, having a family history of malignancy has been established as a risk factor for many types of malignancies (17). Knowledge about family history regarding malignancies helps risk assessment of an individual since 5-10% of cases are inherited (18). The American Cancer Society recommends identifying people with a family history and motivating them to engage in genetic counselling alongside earlier and/or more intensive cancer screening (19). Accordingly, family historiy for malignancy in BD patients can be helpful to identify patients with increased risk for malignancy and to individualize malignancy screening for prevention and early detection.

In our study, we aimed to evaluate the presence of malignancy in BD patients and their families and to compare the demographics, clinical characteristics and medical treatments of BD patients with and without a family history of malignancy.

MATERIAL AND METHOD

The study protocol was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 01.11.2021, Decision No: E1-21-2125). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this cross-sectional study, patients who were consecutively admitted to our rheumatology outpatient clinic between November and December 2021 and diagnosed with BD according to the 1990 ISGB diagnostic criteria (20) were enrolled. Patients under the age of 18 or who did not agree to participate in the study were excluded. Demographics, smoking status, clinical and laboratory data, comorbid diseases, and family history of malignancy were recorded. A history of malignancy in first and second degree members of the family was considered a positive family history for malignancy. Both malignant and premalignant lesions in BD patients were recorded. In at least two consecutive follow-ups, acute phase elevation without an explanatory reason such as underlying infection was considered as chronic persistent disease. BD was divided into two groups as those with and without a family history of malignancy and compared in terms of clinical features of BD.

For numerical variables their conformity to the normal distribution was evaluated using visual (histogram, normality plots) and analytical (Kolmogorov-Smirnof test, coefficient of variation calculation, skewness/sharpness indices) methods. Comparisons between the two groups were made using Student's t-test for normally distributed numerical variables, Mann-Whitney U test for non-normally distributed numerical variables, and Chi-Square or Fisher's exact tests for categorical variables as appropriate. Statistical significance level was accepted as $p<0.05$.

RESULTS

A total of 98 BD patients were included in the study. The mean age ± SD of the patients was 43.5±12.3 years and 57% were male (n=56). At least one comorbidity was present in 60% (n=59) and the frequency of malignancy was 5% (n=5). In family history; the frequences of BD and malignancy were 28% and 38%, respectively.

Demographic characteristics and comorbidities of BD patients were shown in **Table 1**. In the comparison of BD patients with and without a family history of malignancy, the female sex ratio was found to be significantly higher in patients with a family history of malignancy (65% vs. 29%, p=0.001). Age, smoking history, duration of BD symptoms, duration of BD diagnosis, presence of comorbidities and chronic persistent inflammation parameters were similar between the two groups.

The clinical findings of BD patients and the comparison according to the presence and absence of malignancy in the family were shown in **Table 2**. The frequency of mucocutaneous findings in order was oral ulcer %100, genital ulcer 76%, papulopustular eruption 63%, pathergy test positivity 57%. Except for mucocutaneous findings, arthritis was present in 44%, uveitis in 41%, venous thrombosis in 34%, sacroiliitis in 21%, gastrointestinal system involvement in 9%, central nervous system involvement in 7% and arterial thrombosis in 6%. Renal and cardiac involvement was not present in any of our patients. The incidence of erythema nodosum was significantly higher in the group with a family history of malignancy (60% vs. 33%, p=0.010).

The comparison of the drugs used in the treatment of BD patients according to the presence or absence of malignancy in the family is shown in **Table 3**. Most frequently used drug was colchicine in 91%, followed by conventional disease-modifying antirheumatic drugs (cDMARDs) in 72%, glucocorticoids in 64%, biological DMARDs in 22% and cyclophosphamide in 11%. The frequencies of the immunosuppressive treatments were similar between the groups with and without a family history of malignancy.

Table 1. Demographic and laboratory features of Behçet's disease patients with and without a family history of malignancy

Demographic features	All patients, n=98	Malignancy in family n=37	No malignancy in family n=61	p
Age, year, mean±SD	43.5±12.3	43.9 ±10.4	43.3±13.5	0.802
Male, n (%)	56 (57)	13 (35)	43 (71)	0.001
Smoking, n (%)	41 (42)	14 (38)	27 (44)	0.673
Smoking pack-year, median, IQR	14 (15)	10 (14)	15 (16)	0.868
History of surgery n (%)	53 (54)	19 (51)	34 (56)	0.682
Family history of BD n (%)	27 (28)	10 (27)	17 (28)	0.928
Symptom duration of BD, years, median (IQR)	10.5 (11)	11.0 (14)	11.7 (10)	0.443
Diagnosis time of BD, years, median (IQR)	9 (11)	9 (10)	9 (11)	0.809
Comorbidities and laboratory features				
Any comorbidity, n (%)	58 (59)	23 (62)	35 (57)	0.640
FMF, n (%)	3 (3)	2 (5)	1 (2)	0.555
Thyroid disease, n (%)	9 (9)	4 (11)	5 (8)	0.726
Pre/malignancy, n (%)	5 (5)	3 (8)	2 (3)	0.363
Thrombophilia, n (%)	4 (4)	2 (5)	2 (3)	0.631
Diabetes mellitus, n (%)	17 (17)	8 (22)	9 (15)	0.384
Hypertension, n (%)	28 (29)	12 (32)	16 (26)	0.510
Hyperlipidemia, n (%)	11 (11)	4 (11)	7 (12)	0.919
Asthma/allergic rhinitis, n (%)	10 (10)	4 (11)	6 (10)	>0.999
Ischemic heart disease, n (%)	8 (8)	1 (3)	7 (12)	0.252
Anxiety/depression, n (%)	13 (13)	8 (22)	5 (8)	0.071
Migraine, n (%)	6 (6)	3 (8)	3 (5)	0.670
BMI kg/m2, mean±SD	27.6±5.6	28.2±5.4	27.3±5.4	0.467
Chronic persistent inflammation, n (%)	30 (31)	12 (32)	18 (30)	0.823
HLA-B51 positivity, n (%)	9/26 (35)	3/12 (25)	6/14 (43)	0.429

BD: Behçet disease, FMF: Familial mediterranean fever, BMI: Body mass index

Table 2. Comparison of clinical features of patients with Behçet disease who have a family history of malignancy or not

	All patients, n=98 (%)	Malignancy in family n=37 (%)	No malignancy in family n=61 (%)	p
Oral ulcer	98 (100)	37 (100)	61 (100)	-
Genital ulcer	75 (76)	30 (81)	45 (74)	0.408
Papulopustular eruption	62 (63)	20 (54)	42 (69)	0.141
Erythema nodosum	42 (43)	22 (60)	20 (33)	0.010
Uveitis	40 (41)	11 (30)	29 (48)	0.082
Pathergy positivity	47 (57)	16 (49)	31 (62)	0.224
Arthritis	43 (44)	19 (51)	24 (39)	0.246
Sacroiliitis	21 (21)	8 (22)	13 (21)	0.971
Epididymitis	7/56 (13)	2/13 (15)	5/43 (12)	0.658
Venous thrombosis	33 (34)	10 (27)	23 (38)	0.254
Arterial thrombosis	6 (6)	1 (3)	5 (8)	0.404
Central nervous system involvement	7 (7)	2 (5)	5 (8)	0.707
Gastrointestinal system involvement	9 (9)	2 (5)	7 (12)	0.476

Table 3. Comparison of Behçet's disease treatments in patients with and without a family history of malignancy

Drugs	All patients, n=98 (%)	Malignancy in family n=37 (%)	No malignancy in family n=61 (%)	p
Colchicine	89 (91)	35 (95)	54 (89)	0.476
Glucocorticoid	63 (64)	22 (60)	41 (67)	0.437
NSAID	40 (41)	18 (49)	22 (36)	0.219
cDMARD	71 (72)	25 (68)	46 (75)	0.400
IFN-α	4 (4)	1 (3)	3 (5)	>0.999
Cyclophosphamide	11 (11)	2 (5)	9 (15)	0.199
bDMARD	22 (22)	6 (16)	16 (26)	0.321

NSAID: non steroid antiinflammatory drugs; cDMARD: conventional disease modifying antirheumatic drugs, IFN-α: interferon α; bDMARD: biologic disease modifying antirheumatic drugs

In total, 5 (5%) of 98 patients had malignant or premalignant lesions and all patients were female. The lesions were as follows; two thyroid carcinomas and one renal cell carcinoma, two cervical intraepithelial neoplasia-3 (CIN-3) and one endometrial hyperplasia. Three of them had a family history of malignancy and one had a family history of BD. Time from both symptom and diagnosis of BD onset were over 10 years in all patients except one, and the malignancy diagnosis was made 2-18 years after the onset of BD symptoms. The characteristic features of the patients were shown in **Table 4**.

DISCUSSION

In our study 28% of the BD patients had a family history of BD and 38% had a family history of malignancy. All of the 5 patients who had malignant or premalignant lesions in our study were female and all had solid organ lesions. There was no relationship between the presence of malignancy in the family , the demographic and clinical characteristics, the presence of chronic persistent inflammation and the medical treatments for BD, however a relationship was observed with female gender and incidence of erythema nodosum.

Table 4. Characteristics of 5 Behçet's disease patients with Premalignant/Malignant lesions

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Premalignant/Malignant lesion	Thyroid cancer	CIN-3	Renal cell cancer	Thyroid cancer	Endometrial hyperplasia
Duration time, year	7	1	1	10	1
Age, years	45	40	42	53	30
Gender	Female	Female	Female	Female	Female
Smoking history	Yes	Yes	No	No	Yes
Smoking pack-year	30	2	-	-	5
Family history of malignancy	Colon cancer	Lymphoma, gastric cancer	Pharynx cancer	None	None
BD in the family	No	Yes	No	No	Yes
Comorbidities	HT HL HCV	None	HT DM HL	HL IHD Migrain Depression ANH	PCOS Myoma uteri
Symptom duration of BD, years	20	16	3	25	19
Diagnosis timeof BD, years	20	14	0,5	25	10
BMI, kg/m2	32.0	23.5	31.6	28.3	33.2
Chronic persistent inflammation	No	No	No	No	No
HLA-B51 positivity	NA	NA	Positive	NA	Negative
Clinical features					
Oral ulcer	Yes	Yes	Yes	Yes	Yes
Genital ulcer	Yes	Yes	-	-	Yes
Papulopustular eruption	Yes	-	Yes	Yes	-
Erythema nodosum	Yes	Yes	-	Yes	-
Uveitis	-	Yes	-	-	-
Pathergy positivity	NA	NA	Yes	Yes	Yes
Arthritis	Yes	Yes	-	-	-
Sacroiliitis	-	-	Yes	-	-
Venous thrombosis	-	-	-	DVT	-
Arterial thrombosis	-	-	-	-	-
Central nervous system involvement	-	-	-	-	-
Gastrointestinal system involvement	-	-	-	-	-
Medical treatments					
Colchicine	Yes	Yes	Yes	Yes	Yes
Glucocorticoid	Yes	Yes	-	Yes	-
NSAID	Yes	Yes	Yes	-	-
cDMARD	AZA	SLZ MTX AZA	-	AZA	-
IFN-α	-	-	-	-	-
Cyclophosphamide	-	-	-	-	-
bDMARD	Infliximab	Infliximab	-	-	-

BD: Behcet disease, BMI: Body mass index, CIN-3: Cervical intraepithelial neoplasia-3, HT: Hypertension, HL: Hyperlipidemia, DM: Diabetes Mellitus, IHD: Ischemic heart disease, ANH:Adrenal nodular hyperplasia, PCOS: polycystic ovary syndrome, DVT: Deep vein thrombosis, NA: Non-available, NSAID: non steroid antiinflammatory drugs, cDMARD: conventional disease modifying antirheumatic drugs, IFN-α: interferon α, bDMARD: biologic disease modifying antirheumatic drugs, AZA: Azathioprine, SLZ: Sulfasalazine, MTX: Methotrexate

Hematologic and solid organ malignancies may be seen in the course of BD. The autoimmune nature of BD, chronic use of some immunosuppressive drugs and environmental triggering factors are thought to play a role in the development of malignancy (11,21). In the literature, a study (22) comparing BD patients hospitalized in United States (n=2605) and other inpatients (n=37.5 million) in 2016, the incidence of malignancy was found to be significantly higher in BD than other hospitalized patients (3.26% vs 2.74%, respectively, p<0.0001). In a meta-analysis published by Wang et al (23) in 2019, it was found that the frequencies of hematologic cancers and thyroid cancers were increased in BD patients. In the subgroup analysis of this study, cancer risk was found to be higher in women. Kaklamani et al (9) reported approximately 60 cases of BD were associated with various hematologic malignancies in their literature analysis. They also reported that solid tumours were present in only 2 of 128 BD patients in their study. In another study conducted in Korea (24) various solid tumours were detected in 11 (2.2%) of 506 BD. The authors found a low risk of malignancy in BD compared with the general population in Korea. In a cohort of 387 BD patients in Turkey (25), malignancy was detected in 8 patients (all male) during a follow-up of approximately 20 years. Seven were solid organ tumours and one was lymphoma. The incidence of cancer in male BD patients was similar to that observed in the general population. In another retrospective study published in 2020 (12), including Turkey data, 11 cancer cases (3 females, 8 males) were observed during a median follow-up of 124 months in 451 cases with BD. Of these, 10 were solid tumours and 1 was myelodysplastic syndrome. This study revealed that BD patients had an approximately three times greater risk for cancer compared to the respective age and sex groups (standardized incidence rate (SIR) 2.84, 95% CI 1.50–4.94, p < 0.001). These studies lacked details on malignancy related variables, including smoking, alcohol consumption, body mass index, and family history of malignancy. Malignancy development is associated with non-modifiable risk factors such as family history and gender, and modifiable risk factors such as smoking, alcohol, physical inactivity, and obesity. Knowing a person's family history can help determine the risk of hereditary diseases, such as cancer, where 5% to 10% of cases are inherited (18,26). In our study, all malignant and premalignant lesions were solid organ related and were present in female patients. .

Wang et al. (4) reported that malignancies with BD, especially hematologic malignancies, were generally detected within the first year after the diagnosis of BD, and the incidence gradually decreased thereafter. A possible explanation for this may be the increased diagnostic tests performed in these patients during the period when they were diagnosed with BD, and the patients' caring about their own routine follow-ups. This may lead to earlier detection of existing cancer compared to the general population (11,21). In addition, the fact that hematologic malignancy has a similar pathogenesis to BD and that the development of hematologic malignancy is faster may be related to the earlier emergence compared to solid malignancies (4). In our study, the time elapsed between the duration of BD symptoms and the time of detection of malignancy was at least 2 years. All malignancies in our cohort were solid tumours. Due to the absence of hematologic malignancy in our patient group, our malignancy development time was longer according to the literature.

Studies have been conducted on the immunosuppressive therapies used in BD and the development of malignancy. In a retrospective study conducted in Turkey (10), malignancies developed in 15 (8%) cases in a 25-year follow-up of 198 BD patients using cyclophosphamide. Another study (13) evaluating the effect of immunosuppressants used in BD on the development of malignancy showed that thalidomide treatment was an independent protective factor for cancer risk and cyclophosphamide was associated with high cancer risk. The remaining agents, including glucocorticoids, methotrexate, azathioprine and cyclosporine did not significantly correlate with cancer risk. In a study published in 2020 (12), which includes data from Turkey, azathioprine was also found to reduce the risk of cancer. In the present study, there was no relationship between the treatments used and malignancy in BD and malignancy in the family.

There were two findings that caught our attention in our results. First, the female gender had more family history of malignancy and all of our cases with malignant or premalignant lesions were female. As mentioned above, there were conflicting results in terms of gender and malignancy development in studies regarding BD. There was no data in the literature in terms of family history of malignancy and gender. The second important result is that the rate of erythema nodosum was higher in patients with a family history of malignancy. To the best of our knowledge, there is no data related to this issue in the literature. We thought that this result could be an incidental finding.

The major limitation of our study is the small number of patients. In addition, our short working time may cause selection bias. Due to the fact that the information was obtained from the patients and the hospital registry system, there may be lack of some data , especially in terms of family histories. Based on 5 patients with premalignant and malignant lesions,

it is unlikely to draw any statistical conclusions. Due to the fact that our clinic is atertiary center and due to the pandemic conditions, the fact that BD patients with mild symptoms may not come to routine outpatient clinic controls, and the clinical features of the applicant BD are more complicated, preventing our knowledge from being generalized to all BD patients. In the investigation of family history of malignancy, the history of malignancy in first and second degree family members was accepted as positive. Perhaps, in further studies, further differentiation in terms of malignancy as first-degree, second-degree and third degree relatives may lead to better results. Another limitation of our study is that the clinical features of BD patients were not evaluated with an objective scale and the severity of organ involvements was not quantified. Finally, due to the nature of cross-sectional studies, the inability to detect a temporal connection between familial malignancy and BD patients is another limitation of our study, since both were examined simultaneously.

CONCLUSION

It was noteworthy that in our group of BD patients, the family history of malignancy, which was not questioned in previous studies, was quite prominent. The presence of a family history of malignancy in BD should be questioned in larger and more comprehensive studies in order to more accurately evaluate the relationship between certain demographic characteristics, habits, comorbid diseases, clinical findings and the course of the disease. This can help identify people at potential malignancy risk and individualize plans for cancer prevention and early detection.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 01.11.2021, Decision No: E1-21-2125).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Cakir N, Dervis E, Benian O, et al. Prevalence of Behçet's disease in rural western Turkey: a preliminary report. Clin Exp Rheumatol 2004; 22: 53-5.
2. Fietta P. Behçet's disease: familial clustering and immunogenetics. Clin Exp Rheumatol 2005; 23: 96-105.
3. Yazici Y, Hatemi G, Bodaghi B, et al. Behçet syndrome. Nat Rev Dis Primers 2021; 7: 67.
4. Wang LH, Wang WM, Hsu SM, Lin SH, Shieh CC. Risk of overall and site-specific cancers in Behcet disease: a nation wide population-based study in Taiwan. J Rheumatol 2015; 42: 879-84
5. Na SJ, Kang MJ, Yu DS, et al. Cancer risk in patients with Behçet disease: A nationwide population-based dynamic cohort study from Korea. J Am Acad Dermatol 2018; 78: 464-70
6. Lin Y, Li G, Zheng W, Tian X, Zhang F. Behcet's disease associated with malignancy: a report of 41 Chinese cases. Int J Rheum Dis 2014; 17: 459-65
7. Cengiz M, Altundag MK, Zorlu AF, Güllü IH, Ozyar E, Atahan IL. Malignancy in Behçet's disease: a report of 13 cases and a review of the literature. Clin Rheumatol 2001; 20: 239-44.
8. Tada Y, Koarada S, Haruta Y, Mitamura M, Ohta A, Nagasawa K. The association of Behçet's disease with myelodysplastic syndrome in Japan: a review of the literature. Clin Exp Rheumatol 2007; 25: 507-8
9. Kaklamani VG, Tzonou A, Kaklamanis PG. Behçet's disease associated with malignancies. Report of two cases and review of the literature. Clin Exp Rheumatol 2005; 23: 35-41.
10. Gurcan M, Esatoglu SN, Hamuryudan V, et al. Long term follow-up of Behçet's syndrome patients treated with cyclophosphamide. Rheumatology (Oxford) 2020; 59: 2264-71.
11. Martin DN, Mikhail IS, Landgren O. Autoimmunity and hematologic malignancies: associations and mechanisms. Leuk Lymphoma 2009; 50: 541-50
12. Guven DC, Bolek EC, Altintop SE, et al. Cancer incidence in Behçet's disease. Ir J Med Sci 2020 ; 189: 1209-14.
13. Huang MX, Wang CY, Guo JY, et al. Pharmacotherapy for Behçet's Disease and the Risk of Malignancy. Front Pharmacol 2021; 12: 661150.
14. . Uçar F, Sönmez M, Ermantaş N, et al. The associations of HLA-A, -B, DRB1 alleles and haplotypes in Turkish lymphoma patients. Gene 2016; 586 : 263-7.
15. Xiao X, Liu L, Li WJ, Liu J, Chen DJ. HLA-A, HLA-B, HLA-DRB1 polymorphisms and risk of cervical squamous epithelial cell carcinoma: a population study in China. AsianPac J CancerPrev 2013; 14: 4427-33.
16. Shuxian J, Xiaoyun C, Zhihui F, et al. Association of HLA-B*51: 01 with papillary thyroid carcinoma in the Chinese Han population of the Shandong coastal areas. Thyroid 2014; 24: 867-71.
17. Sieverding M, Arbogast AL, Zintel S, von Wagner C. Gender differences in self-reported family history of cancer: A review and secondary data analysis. Cancer Med 2020; 9: 7772-80.
18. Krakow M, Rising CJ, Trivedi N, Yoon DC, Vanderpool RC. Prevalence and correlates of family cancer history knowledge and communication among US adults. Prev Chronic Dis 2020; 17: 146.
19. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2018; 68: 297-316.
20. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet 1990; 335: 1078-80.
21. Baecklund E, Smedby KE, Sutton LA, Askling J, Rosenquist R. Lymphoma development in patients with autoimmune and inflammatory disorders—whatare the driving forces? Semin Cancer Biol 2014; 24: 61-70.

22. Naramala S, Konala VM, Adapa S, et al. Trends in hospitalization and inpatient outcomes of behçet's disease: a nationwide inpatient sample study. Cureus 2020; 12: 7470.

23. Wang X, Peng Y, Gao J, Han S, Li Y. Risk of malignancy in Behcet disease: a meta-analysis with systematic review. Medicine (Baltimore) 2019; 98: 17735.

24. Na SY. Morbidity of solid cancer in Behcet's disease: analysis of 11 cases in a series of 506 patients. Yonsei Med J 2013; 54: 895–901.

25. Kural-Seyahi E, Fresko I, et al. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine (Baltimore) 2003; 82: 60-76.

26. Hidaka A, Sawada N, Svensson T, et al; JPHC Study Group. Family history of cancer and subsequent risk of cancer: A large-scale population-based prospective study in Japan. Int J Cancer 2020; 147: 331-7.

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The role of inflammatory markers derived from complete blood count results in the diagnosis of intrahepatic cholestasis of pregnancy

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ABSTRACT

Objective: This study aimed to investigate complete blood count (CBC) markers, particularly those indicating systemic inflammation, in healthy subjects and those with mild and severe intrahepatic cholestasis of pregnancy (ICP).

Material and Method: Seventy-nine subjects with ICP and 100 healthy age-matched women who were matched based on their scheduled singleton deliveries (on the same day) were included. ICP was defined as the increase in serum bile acid levels ≥10 μmol/L coupled with pruritus which could not be explained by other conditions. Patients with ICP were further categorized to mild and severe ICP according to bile acid levels, as follows: Mild ICP (<40 μmol/L, n=55) and severe ICP (≥40 μmol/L, n=24). Venous blood samples were drawn upon admission to analyze bile acid concentration, liver enzymes and CBC.

Results: Mean platelet volume (MPV) was similar in subjects with mild and severe ICP whose values were higher than that of controls ($p<0.001$). The red cell distribution width (RDW) of subjects with severe ICP was lower compared to controls, although no significant difference existed between the mild and severe ICP groups. Platelet to lymphocyte ratio (PLR) was higher in subjects with mild and severe ICP compared to controls, but it was similar in mild and severe ICP. There were no significant differences in neutrophil to lymphocyte ratio (NLR) between the groups. Correlation analysis revealed that bile acid, bilirubin, AST and ALT levels were correlated positively with MPV and PLR, and negatively with RDW value. MPV was also positively correlated with the length of stay in ICU (intensive care unit). ROC (Receiver Operating Characteristic) curve analysis showed that MPV and PLR could discriminate subjects with ICP from controls with a high sensitivity but relatively low specificity. However, neither NLR nor PLR were sensitive for discriminating severe ICP from mild ICP.

Conclusions: Some CBC derived parameters associated with inflammatory state, such as MPV and PLR, appear to have value for ICP diagnosis. However, MPV, NLR, PLR, RDW, and leukocyte count cannot be used for the discrimination of mild and severe ICP.

Keywords: Markers, cholestasis, pregnancy

INTRODUCTION

Cholestasis is historically defined as a limitation in bile flow owing to impaired secretion by hepatocytes or to obstruction of bile flow through intra- or extra-hepatic bile ducts (1). Clinical presentation of a patient with cholestasis may vary due to the retained bile component. Cholestasis of pregnancy is an intrahepatic disorder specific to pregnancy which typically presents in the third trimester and resolves rapidly following delivery (2, 3). The etiology of intrahepatic cholestasis of pregnancy (ICP) is not well understood; however, several genetic, environmental, and hormonal factors are believed to contribute to the development of ICP (4).

Although ICP resolves following delivery, accumulating data has shown that it can also be associated with spontaneous and iatrogenic preterm labor, meconium-stained amniotic fluid, fetal hypoxia, and stillbirth (5, 6). Increase of bile acids in fetal and placental circulation is considered to play a role in development of adverse fetal outcomes (7). Previous data indicate that subjects with severe ICP, characterized with a higher increase in bile acids, more frequently encounter fetal complications compared to subjects with mild ICP (8).

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A recent study has shown that systemic inflammation could be associated with the etiology of ICP. Leukocyte count, platelet to lymphocyte ratio (PLR), and mean platelet volume (MPV), which are components of a simple complete blood count (CBC) test were found to be increased in subjects with ICP compared to controls (9). However, there is still paucity in evidence concerning the role of inflammation in subjects with ICP.

In this study, we aimed to investigate CBC markers that have been associated with systemic inflammation in healthy subjects and patients with mild and severe ICP, and to assess whether these parameters could be used for diagnostic purposes.

MATERIAL AND METHOD

The study was approved by University of Health Sciences Kanuni Sultan Süleyman Training and Researches Hospital Clinical Research Ethics Committee (Date:10.12.2020, Decision No: KAEK/2020.12.210). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The present cross-sectional study was conducted at the Kanuni Sultan Suleyman Training and Research Hospital Department of Gastroenterology and Rumeli Hospital Department of Obstetric and Gynecology, Istanbul, Turkey between 02.03.2021 and 15.07.2021. All subjects provided written informed consent before enrollment. Seventy-nine subjects with ICP and 100 healthy age-matched women who were matched based on their scheduled date of singleton delivery (same dates as the patient group) were selected for the study. ICP was defined as an increase of ≥10 μmol/L in serum bile acid levels in the presence of pruritus which could not be explained by any other clinical condition. Patients with any acute or chronic inflammatory disease (rheumatoid arthritis or inflammatory bowel disease) and those with conditions which may lead to increase in liver enzymes and bile acids (Wilson's disease, cholecystitis, primary sclerosing cholangitis, primary biliary cirrhosis, alpha-1-antitrypsin deficiency, symptomatic cholelithiasis, cytomegalovirus, Epstein-Barr virus infection, autoimmune hepatitis, or acute fatty liver of pregnancy) and those with HELLP syndrome were excluded. All patients with ICP received ursodeoxycholic acid (UDCA) treatment. Patients' demographic and clinical characteristics (including self-reported itching frequency) were also recorded.

Patients with ICP were further categorized into mild and severe ICP according to bile acid levels, as per the following definitions: mild ICP (<40 μmol/L, n=55) and severe ICP (≥40 μmol/L, n=24). Venous blood samples were acquired to measure bile acid concentration, liver enzymes (GEN-S; Beckman-Coulter, Brea, CA, USA) and complete blood count (Cell-Dyn 3700; Abbott, USA). Patients were started on UDCA treatment after diagnosis, and therefore, follow-up blood samples were also withdrawn to assess bile acid concentration and liver enzymes. The samples were centrifuged at 2000 × g for 10 min within 5–10 min of blood sampling, and analyses were conducted immediately. Serum total bile acid concentration was measured via spectrophotometry using an enzymatic method on a Cobas C501 Analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

The primary outcome measure of this study was to investigate the difference in CBC derived parameters indicating acute inflammation, including leukocyte count, neutrophil to lymphocyte ratio (NLR), red blood cell distribution width (RDW), and PLR between patients with and without ICP and between patients with and without severe ICP.

Statistical Analysis

Analyses were performed with SPSS v25 (SPSS Inc., Chicago, IL, USA) and significance was defined as a p value of <0.05. Histogram and Q-Q plots were used to determine quantitative variable distribution features. Data concerning continuous variables are given as mean±standard deviation or median (1st quartile-3rd quartile) (according to normality of distribution); whereas categorical variables were depicted with frequency (percentage) values. Normally distributed variables were analyzed with the independent samples t-test or one-way analysis of variance (ANOVA) depending on group count. Non-normally distributed variables were analyzed with the Mann-Whitney U test or Kruskal Wallis test depending on group count. Categorical variables were analyzed with the chi-square tests or Fisher's exact tests. Pairwise corrections employed the Bonferroni correction. Repeated measurements were analyzed with the Wilcoxon signed ranks test. Pearson, Spearman or point-biserial correlation coefficients were calculated to evaluate relationships between markers and other variables. Prediction performance of the markers were assessed by using Receiver Operating Characteristic (ROC) curve analysis.

RESULTS

A total of 79 patients with ICP (mean age 29.79±5.84 years) and 100 controls were enrolled in this study. Of the subjects with ICP, 55 were classified as mild ICP (mean age 29.82±5.73 years) and 24 were classified as severe ICP (mean age 28.71±6.01 years). Patients with ICP had greater gestational age (p<0.001), higher bile acid concentration before (p<0.001) and after UDCA treatment (p=0.038). Additionally, these patients had

higher aspartate transaminase (AST, p<0.001) and alanine transaminase (ALT, p<0.001) levels and higher total (p<0.001) and direct bilirubin levels (p<0.001) compared to control subjects. Subjects with severe ICP more frequently experienced severe itching compared to those with mild ICP. Although AST, ALT, gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) levels were similar in mild and severe ICP, direct bilirubin was significantly higher in those with severe ICP compared to the mild ICP group [0.41 (0.29-0.64) mg/dl vs. 0.20 (0.12-0.40) mg/dl, p<0.00].

Comparison of CBC parameters between the groups is presented in **Table 1** and **2**. Platelet count of subjects with ICP was higher than that of controls (p<0.001); however, there were no significant differences in platelet count between the severe and mild ICP groups. The leukocyte count of subjects with severe ICP was lower than that of the controls, but values were similar in controls and subjects with mild ICP. Mean platelet volume (MPV) was similar in subjects with mild and severe ICP and was higher than that of controls (p<0.001). Red cell distribution width (RDW) of subjects with severe ICP was lower than the RDW of the controls, while the mild and severe ICP groups were similar in this respect. Platelet to lymphocyte ratio (PLR) was higher in subjects with ICP compared to controls, but the mild and severe ICP groups had similar values. There were no significant differences in neutrophil to lymphocyte ratio (NLR) between the groups. Newborns who were born to mothers with ICP had longer intensive care unit (ICU) stay and lower birth weights compared to newborns born to healthy mothers.

Correlation analysis revealed that MPV and PLR were positively, and RDW was negatively correlated with bile acid concentration, bilirubin, and AST and ALT levels. MPV was also positively correlated with the length of stay in ICU (**Table 3**). ROC curve analysis revealed that MPV (cut-off: 9.7) and PLR (cut-off: 107.2) could discriminate subjects with ICP from controls with high sensitivity but relatively low specificity (**Table 4, Figure 1**). However, neither NLR nor PLR were sensitive for the discrimination of severe ICP from mild ICP (**Table 5**, **Figure 2**).

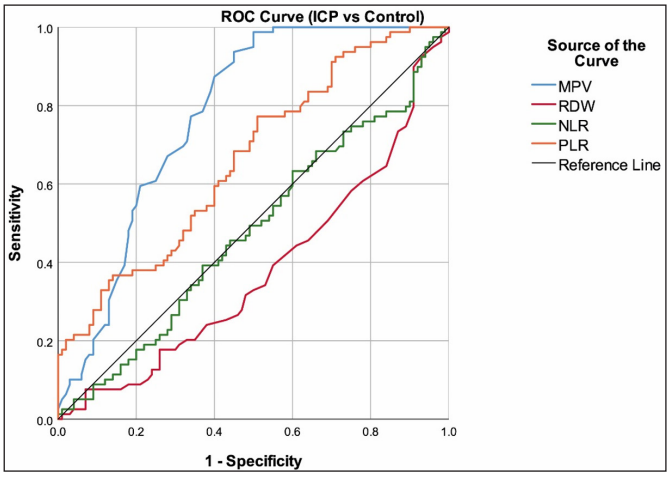

Figure 1. Receiver operating characteristic (ROC) curves of study variables to discriminate ICP patients from controls

Table 1. Summary of patient characteristics with regard to groups

	Groups			p
	Control (n=100)	Mild ICP (n=55)	Severe ICP (n=24)	
Age	29.18±5.30	29.82±5.73	28.71±6.01	0.670
Gestational week	27.5 (23-30) [a]	33 (31-35) [b]	32.5 (31-34) [b]	**<0.001**
Number of pregnancy	-	2 (1-3)	2.5 (1-4)	0.921
Pregnancy				0.661
Singleton	-	50 (90.91%)	23 (95.83%)	
Twin	-	5 (9.09%)	1 (4.17%)	
Bile acid				
Initial	5 (4-7) [a]	17 (12-25) [b]	60.5 (47.5-84.5) [c]	**<0.001**
After UDCA	-	3 (3-4)	4 (3-4)	**0.038**
p (within groups)	N/A [A]	**<0.001**	**<0.001**	
Itching				**0.003**
None	-	2 (3.64%)	0 (0.00%)	
Mild	-	9 (16.36%)	0 (0.00%)	
Moderate	-	18 (32.73%)	2 (8.33%)	
Severe	-	26 (47.27%)	22 (91.67%)	
Pruritus regression with UDCA	-	39 (70.91%)	15 (62.50%)	0.634
Intrauterine / Neonatal death	0 (0.00%)	2 (3.64%)	0 (0.00%)	0.102
Birth week	38 (37-39) [a]	37 (37-38) [b]	37 (36-37.5) [b]	<0.001
Type of birth				0.108
Natural	-	26 (47.27%)	6 (25.00%)	
Cesarean	-	29 (52.73%)	18 (75.00%)	
Birth weight	3214.7±464.61 [a]	2810.51±554.20 [b]	2776.30±590.88 [b]	<0.001
Length of stay in ICU	1 (1.00%) [a]	11 (20.00%) [b]	6 (25.00%) [b]	<0.001

Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. a,b: Same letters denote the lack of statistically significant difference between groups. Abbreviations: N/A: Not applicable, ICU: Intensive care unit, UDCA: Ursodeoxycholic acid

Table 2. Summary of patient laboratory measurements with regard to groups

ALT (IU/mL)				
Initial	12 (9-14) [a]	62 (40-117) [b]	147.5 (69-243.5) [b]	<0.001
After UDCA	-	43 (24-65)	49 (33.5-107.5)	0.129
p (within groups)	N/A	<0.001	0.001	
AST (IU/mL)				
Initial	14 (12.45-18) [a]	48 (35-70) [b]	77 (45-139.5) [b]	<0.001
After UDCA	-	31.5 (22.5-40.5)	34 (22-58)	0.339
p (within groups)	N/A	<0.001	0.001	
Total bilirubin (mg/dL)	0.24 (0.15-0.30) [a]	0.40 (0.29-0.70) [b]	0.64 (0.41-0.78) [b]	<0.001
Direct bilirubin (mg/dL)	0.13 (0.11-0.18) [a]	0.20 (0.12-0.40) [b]	0.41 (0.29-0.64) [c]	<0.001
ALP (IU/L)	-	195.84±60.01	222.63±74.89	0.095
GGT (IU/L)	-	15 (11-26)	18.5 (11-27)	0.725
LDH (IU/L)	-	222.94±46.65	223.79±43.66	0.940
Hemoglobin (g/dL)	11.35±1.59	11.56±1.36	11.56±1.14	0.638
Platelet (×10³/mm³)	210.82±67.27 [a]	243.82±67.95 [b]	270.96±76.23 [b]	<0.001
WBC (×10³/mm³)	10.73±2.89 [a]	10.15±2.54 [ab]	9.07±1.62 [b]	0.001
Neutrophil (×10³/mm³)	7.93±2.64 [a]	7.45±2.24 [ab]	6.51±1.63 [b]	0.006
Lymphocyte (×10³/mm³)	1.95±0.55	1.83±0.54	1.89±0.43	0.380
MPV (µm³)	9.39±1.78 [a]	11.07±1.13 [b]	11.05±1.06 [b]	<0.001
RDW (%)	13.65 (13.05-15.2) [a]	13.2 (12.8-14.6) [ab]	13.05 (12.6-13.5) [b]	0.005
Neutrophil lymphocyte ratio	3.92 (3.01-5.15)	4 (3.06-5.14)	3.43 (2.59-4.34)	0.202
Platelet lymphocyte ratio	109.8 (83.68-143.9)[a]	126.25(107.39-173.9)[b]	124.4(108.23- 212.14)[b]	0.001

Table 3. Correlations between MPV, RDW, NLR, PLR and other variables

		MPV	RDW	NLR	PLR
Age	r	0.016	-0.065	0.049	-0.040
	p	0.832	0.385	0.517	0.596
Gestational week	r	0.370	-0.101	-0.071	0.134
	p	<0.001	0.179	0.347	0.075
Number of pregnancy	r	-0.074	-0.005	-0.012	0.141
	p	0.517	0.962	0.919	0.216
Bile acid	r	0.409	-0.230	-0.074	0.223
	p	<0.001	0.002	0.323	0.003
Itching	r	0.113	-0.158	-0.007	0.063
	p	0.321	0.165	0.954	0.580
ALT (IU/mL)	r	0.461	-0.223	-0.094	0.264
	p	<0.001	0.003	0.209	<0.001
AST (IU/mL)	r	0.442	-0.165	-0.091	0.278
	p	<0.001	0.028	0.225	<0.001
Total bilirubin (mg/dL)	r	0.185	-0.146	-0.057	0.164
	p	0.013	0.051	0.448	0.029
Direct bilirubin (mg/dL)	r	0.101	-0.191	-0.035	0.180
	p	0.178	0.011	0.644	0.016
ALP (IU/L)	r	-0.086	-0.002	0.022	0.188
	p	0.451	0.987	0.847	0.097
GGT(IU/L)	r	-0.067	-0.008	-0.201	-0.029
	p	0.563	0.944	0.080	0.800
LDH (IU/L)	r	0.093	-0.109	-0.053	-0.030
	p	0.419	0.346	0.647	0.793
Duration of stay in ICU	r	0.265	-0.061	0.034	0.052
	p	<0.001	0.415	0.655	0.491

r: Correlation coefficient, Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase LDH: Lactate Dehydrogenase, ICP: Intrahepatic cholestasis of pregnancy, ICU: Intensive care unit, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MPV: Mean platelet volume, RDW: Red Cell Distribution Width

Table 4. Performance of markers to discriminate patients with ICP from healthy controls

	MPV	RDW	NLR	PLR
Cut-off	≥ 9.7	≥ 13.5	≥ 3.5	≥ 107.2
Sensitivity	93.67%	39.24%	63.29%	77.22%
Specificity	55.00%	45.00%	40.00%	49.00%
Accuracy	72.07%	42.46%	50.28%	61.45%
PPV	62.18%	36.05%	45.45%	54.46%
NPV	91.67%	48.39%	57.97%	73.13%
AUC (95.0% CI)	0.777 (0.709-0.845)	0.378 (0.295-0.460)	0.479 (0.393-0.565)	0.662 (0.583-0.741)
p	<0.001	N/A	N/A	<0.001

Abbreviations: PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, MPV: Mean platelet volume, RDW: Red Cell Distribution Width, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, N/A: Not applicable (p values are not calculated due to AUC is below 0.5)

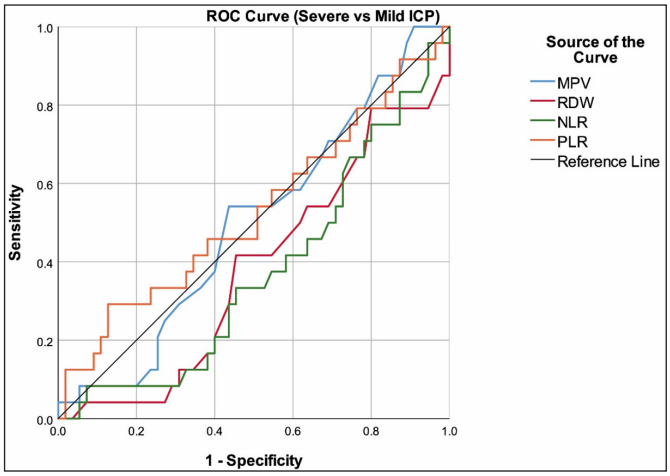

Figure 2. Receiver operating characteristic (ROC) curves of study variables to discriminate mild ICP patients from severe.

Table 5. Performance of markers to discriminate mild and severe ICP

	MPV	RDW	NLR	PLR
Cut-off	≥ 11.2	≥ 13.4	≥ 3.75	≥ 140
Sensitivity	54.17%	41.67%	41.67%	45.83%
Specificity	56.36%	54.55%	41.82%	61.82%
Accuracy	55.70%	50.63%	41.77%	56.96%
PPV	35.14%	28.57%	23.81%	34.38%
NPV	73.81%	68.18%	62.16%	72.34%
AUC (95.0% CI)	0.500 (0.365-0.635)	0.381 (0.250-0.512)	0.373 (0.242-0.504)	0.528 (0.383-0.673)
p	0.996	N/A	N/A	0.693

Abbreviations: PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, MPV: Mean platelet volume, RDW: Red Cell Distribution Width, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, N/A: Not applicable (p values are not calculated due to AUC is below 0.5)

DISCUSSION

This study demonstrates that patients with ICP had higher MPV, platelet count and PLR, but similar NLR compared to controls. Subjects with mild and severe ICP were similar with respect to the great majority of variables analyzed. In addition, bile acids, AST, ALT and bilirubin levels were correlated with RDW (inversely) and MPV and PLR (positively). MPV and PLR appear to be sensitive for the discrimination of patients with ICP from healthy subjects; however, CBC derived parameters could not discriminate patients in terms of ICP severity.

Intrahepatic cholestasis of pregnancy is recognized by elevation in bile acid concentrations and transaminase levels in addition to unexplained pruritus, particularly after the 30th gestational week (4,10). ICP spontaneously resolves rapidly following delivery. However, ICP has been shown to be related to fetal adverse outcomes, including preterm labor, fetal distress, low birthweight, intrauterine fetal death, and perinatal mortality correlating with the severity of cholestasis (11). Although the exact mechanism underlying ICP has not been clearly understood yet, multiple factors including nutritional deficiency, hormonal changes, environmental and genetic variations have been reported to take part in development of ICP (12-14).

Recent data have shown that inflammation and inflammatory processes may also contribute to ICP (15-18). During the course of cholestasis, inflammation-induced lipopolysaccharides are cleared by the hepatocytes and Kupfer cells produce increased amounts of proinflammatory cytokines (19). In addition, bile acids can directly activate signaling pathways in hepatocytes that stimulate production of proinflammatory mediators (20). Recently, the study of Biberoglu et al. (15) has reported that serum IL-6 level was upregulated in subjects with ICP, although no significant difference was observed between subjects with mild and severe ICP (15). Accumulated data has revealed that simple and readily available CBC derived parameters, including MPV, NLR, PLR, RDW, and leukocyte count, can be used to determine the presence of an inflammatory state particularly in patients with cardiovascular disorders. Since the prenatal complications and fetal adverse events increase with the severity of cholestasis in ICP, estimating the severity of ICP and discriminating mild ICP from severe ICP is critical to prevent prenatal events. For this purpose, Abide et al. studied CBC derived parameters in subjects with ICP and found that PLR, MPV and leukocyte count was increased and RDW was decreased in subjects with ICP. MPV was also significantly higher in subjects with ICP compared to those with mild ICP. The authors concluded that MPV could be utilized to discriminate severe ICP from mild ICP (9). However, the role of CBC markers, particularly those believed to indicate inflammation such as leukocyte count, NLR, PLR, and MPV is still a matter of debate.

Our findings demonstrate that MPV and PLR are higher in subjects with ICP, and that these markers are correlated with the bile acid concentration, AST, ALT and bilirubin levels. Moreover, MPV and PLR have high sensitivity for discriminating subjects with ICP form controls. However, none of the CBC derived parameters including leukocyte count, NLR, PLR, and MPV demonstrate neither sensitivity nor specificity for discriminating mild ICP form severe ICP, which conflicts with the study by Abide et al.; however, our inclusion/exclusion criteria and the fact that we matched patients and controls with respect to expected delivery date are some of the important advantages of our study. With this background in mind, we consider that MPV and PLR can be utilized for discrimination of ICP from healthy controls. However, further research with larger study population is required to address the role of MPV and PLR in the evaluation of ICP severity.

There are some limitations to be mentioned. The cross-sectional design of the study limits further evaluation of perinatal outcomes. Second, lack of other simple markers of inflammation including C-reactive protein and IL-6 levels is an important limitation concerning the assessment of inflammation in ICP. Further prospectively designed studies with larger sample sizes that provide more detailed monitoring of perinatal complications may improve the knowledge concerning the role of inflammatory markers in the severity of ICP.

CONCLUSION

Some inflammation-related CBC derived parameters, such as MPV and PLR, can be utilized to address the presence of ICP with high sensitivity but low specificity. However, there appears to be no role for MPV, NLR,

PLR, RDW, and leukocyte count in the discrimination of mild and severe ICP. Further prospective studies with larger sample size may provide additional information regarding the usefulness of these markers in ICP.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date:10.12.2020, Decision No: KAEK/2020.12.210).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol 2014; 124: 120-33.
2. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009; 15: 2049-66.
3. Marschall HU. Management of intrahepatic cholestasis of pregnancy. Expert Review of Gastroenterol Hepatol 2015; 9: 1273-9.
4. Smith DD, Rood KM. Intrahepatic cholestasis of pregnancy. Clin Obstet Gynecol 2020; 63: 134-51.
5. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology (Baltimore, Md). 2004; 40: 467-74.
6. Lee RH, Kwok KM, Ingles S, et al. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol 2008; 25: 341-5.
7. Ovadia C, Williamson C. Intrahepatic cholestasis of pregnancy: recent advances. Clinics in Dermatology 2016; 34: 327-34.
8. Brouwers L, Koster MP, Page-Christiaens GC, et al. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Am J Obstet Gynecol 2015; 212: 100. e1-7.
9. Yayla Abide Ç, Vural F, Kılıççı Ç. et al. Can we predict severity of intrahepatic cholestasis of pregnancy using inflammatory markers? Turk J Obstet Gynecol 2017; 14: 160-5.
10. Dixon PH, Williamson C. The pathophysiology of intrahepatic cholestasis of pregnancy. Clinics and Research in Hepatol Gastroenterol 2016; 40: 141-53.
11. Bicocca MJ, Sperling JD, Chauhan SP. Intrahepatic cholestasis of pregnancy: Review of six national and regional guidelines. Eur J Obstet Gynecol Reproductive Biology 2018; 231: 180-7.
12. Floreani A, Gervasi MT. New insights on intrahepatic cholestasis of pregnancy. Clin Liver Dis 2016; 20: 177-89.
13. Palmer KR, Xiaohua L, Mol BW. Management of intrahepatic cholestasis in pregnancy. Lancet (London, England) 2019; 393: 853-4.
14. Wood AM, Livingston EG, Hughes BL, Kuller JA. Intrahepatic cholestasis of pregnancy: review of diagnosis and management. Obstet Gynecol Survey 2018; 73: 103-9.
15. Biberoglu E, Kirbas A, Daglar K, et al. Role of inflammation in intrahepatic cholestasis of pregnancy. J Obstet Gynaecol Research 2016; 42: 252-7.
16. Kirbas A, Biberoglu E, Ersoy AO, et al. The role of interleukin-17 in intrahepatic cholestasis of pregnancy. J Maternal-Fetal Neonatal Med 2016; 29: 977-81.
17. Temel Yüksel İ, Aslan Çetin B, Köroğlu N, Aydoğan Mathyk B, Erdem B. Inflammatory marker YKL-40 levels in intrahepatic cholestasis of pregnancy. Gynecol Endocrinol 2019; 35: 635-7.
18. Vural Yilmaz Z, Gencosmanoglu Turkmen G, Daglar K, Yılmaz E, Kara O, Uygur D. Elevated red blood cell distribution width is associated with intrahepatic cholestasis of pregnancy. Ginekologia Polska 2017; 88: 75-80.
19. Kosters A, Karpen SJ. The role of inflammation in cholestasis: clinical and basic aspects. Seminars in Liver Disease 2010; 30: 186-94.
20. Allen K, Jaeschke H, Copple BL. Bile acids induce inflammatory genes in hepatocytes: a novel mechanism of inflammation during obstructive cholestasis. Am J Pathol 2011; 178: 175-86.

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Does face mask affects sleep quality in patients with nasal septal deviation: evaluated by mini sleep questionnarie

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ABSTRACT

Objectives: The aim of this study was to investigate the effects of face mask usage on the sleep quality of patients with nasal septal deviation.

Material and Method: Thirty-four patients with unilateral nasal septum deviation (Group 1) and 27 healthy subjects without septum deviation (Group 2, control) were included in the study. Mask usage time per day (hours) in the last week, weight, length and BMI values, smoking, and alcohol habits were asked. In both groups, the sleep quality of the patients was evaluated by Mini Sleep Questionnaire (MSQ). Sleep delay (SD), sleep awakenings (SA), sleep medications (SM), daytime sleep (DS), morning fatigue (MF), habitual snoring (HS), morning awakening (MA), morning headache (MH), chronic fatigue (CF), and restless sleep (RS); and total MSQ items were evaluated.

Results: All subjects used surgical masks. In the nasal septal deviation group, the right-sided deviation was detected in 15 (44.1%) patients and left-sided deviation was detected in 19 (55.9%) patients. Deviation located was anterior deviation in 12 (35.3%) patients, posterior deviation in 13 (38.2%) patients and antero-posterior deviation in 9 (26.5%) patients. Sleep Medications (SM) and Morning Headache (MH) values of the deviation group (Group 1) were significantly lower than those in the control group ($p<0.05$). There was no difference between other MSQ items and total MSQ score of the septal deviation and control groups ($p>0.05$). In older patients with septal deviation, Sleep Awakenings (SA), Habitual Snoring (HS), Morning Awakening (MA), and Total MSQ scores increased ($p<0.05$)

Conclusion: Facial mask usage did not cause sleep disorders in patients with nasal septal deviation. However, aging may cause disturbed sleep quality.

Keywords: Facial mask, surgical mask, nasal septal deviation, mini sleep questionnaire (MSQ).

INTRODUCTION

Sleep is a physiological, psychological, and social need. The basic and indispensable daily life activity that affects the quality of life and is essential for the health of individuals. The importance of sleep applies to all ages. Sleep disorders are quite common in the population. In a study conducted in the USA, its prevalence was foundto be 30% on average (1).

The importance of sleep is an issue that has come to the fore in recent years. Sleep disorder is an important pathology that affects the quality of life, daily life, and the work-life all at once. While we have objective surveys to test sleep disorders (polysomnography etc.), subjective tests and questionnaires are also frequently used (1).

The Mini-Sleep Questionnaire (MSQ) is a subjective test developed by Zomer et al. (2) for screening sleep disturbances in large populations. Although the questionnaire is used in large populations, there have been examples of it used in limited populations (3). It is a test that is easy to use and evaluate and does not force the participating patients. It contains 10 questions and the answers are scored with 1, 4, 7, respectively, and statistical evaluation is made (2).

Nasal obstruction is a common condition in patients presenting to the ear-nose-throat clinics.

The most common cause of nasal obstruction is septum deviation. In studies conducted, it was stated that nasal deformities and the most common cause of septum deviation are seen with an average of 70% prevalence (3). Getting less sleep was reported in a third of adults. Sleep disorders may cause an increase in health problems of the persons (5). However, causes of nasal obstruction are the leading causes of sleep disorders (6-9).

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While surgical masks are common equipment used by healthcare professionals, they have turned into equipment commonly used by the entire population with the COVID-19 pandemic. At the beginning of the study, the effect of using a face mask on sleep quality was investigated in patients with and without nasal septal deviation, predicting that there may be decreases in sleep quality with nasal masks. Another hypothesis was that the negative effect of septal deviation on sleep could be further increased by facial mask.

MATERIALS AND METHOD

The study was carried out with the permission of Kırıkkale University Non-interventional Researches Ethics Committee (Date: 09.12.2022, Decision No: 2021.12.17). All steps were performed according to the rules outlined in the Declaration of Helsinki. Written consent was obtained from all subjects to participate in the study. Study data were collected between 10.12.2021 and 20.01.2022.

Subjects

Thirty-four patients (18 males and 16 females), applied to Kırıkkale University Medical Faculty, otorhinolaryngology policlinics and were diagnosed with unilateral nasal septum deviation were included as the study group (Group 1). The mean age of the patients in Group 1 was 32.23± 11.34 years (Ranging from 18 to 60 years). The flow diagram is shown in **Figure 1**.

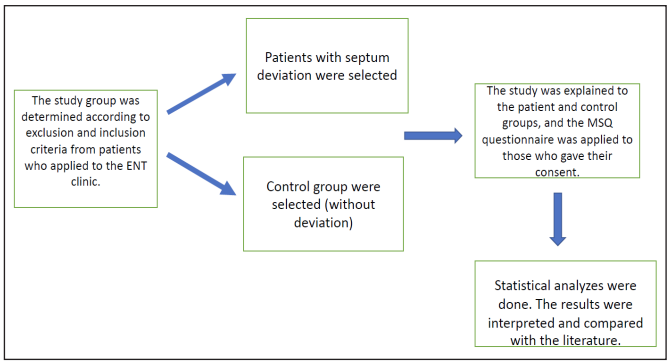

Figure 1. Flow diagram of study

Twenty-seven healthy subjects (11 males and 16 females) without septum deviation were included in the control group (Group 2). The mean age of the patients in Group 2 was 27.33±7.94 years (Ranging from 18 to 43 years).

Mask usage time per day (hours) in the last week was asked. All subjects in group 1 and 2, weight, length and BMI values, smoking, and alcohol habits were asked. All subjects used surgical masks.

Exclusion Criteria

Patients with chronic diseases, inferior turbinate hypertrophy, bilateral nasal septal deviation, nasal polyps, a nasal mass, psychiatric illness, chronic obstructive lung diseases were excluded from the study.

Inclusion Criteria

Patients with unilateral nasal septum deviation, routine use of nasal mask during the day, age of 18-65 years were included in study.

Patients who wanted to withdraw from the study and whose additional diseases were determined were excluded from the study, which created a difference in the number of patients between the groups.

Mini Sleep Questionnaire (MSQ)

A 10-point MSQ focused entirely on sleep quality. This questionnaire consisted of questions concerning actors disturbing or affecting sleep, with responses indicated on a frequency scale of 1-7 (1=never, 4 =sometimes, 7=always). Mean scores in normal sleepers across different age groups were 2.1-2.5 with a standard deviation of 1.3 or1.4. Items of the 10-point MSQ are:1) Sleep delay (SD), 2) sleep awakenings (SA), 3) sleep medications (SM), 4) daytime sleep (DS), 5) morning fatigue (MF), 6) habitual snoring (HS), 7) morning awakening (MA), 8) morning headache (MH), 9) chronic fatigue (CF), and 10) restless sleep (RS) (see **Appendix 1**) (1).

Appendix 1: Mini Sleep Questionnaire (MSQ)1		
Name - Surname:	**Telephone:**	**Date:**
1. Have you had difficulties in falling asleep? (SD: Sleep Delay)		
a) Never	b) Sometimes	c) Always
2. How often have you awakened at night? (SA: Sleep Awakenings)		
a) Never	b) Sometimes	c) Always
3. Do you use sleeping pills? (SM: Sleep Medications)		
a) Never	b) Sometimes	c) Always
4. Do you feel excessively sleepy during the daytime? (DS: Daytime Sleep)		
a) Never	b) Sometimes	c) Always
5. Do you wake up in the morning tired? (MF: Morning Fatique)		
a) Never	b) Sometimes	c) Always
6. Do you snore during sleep? (HS: Habitual Snoring)		
a) Never	b) Sometimes	c) Always
7. How often have you awakened too early in the morning without being able to fall asleep again? (MA: Morning Awakening)		
a) Never	b) Sometimes	c) Always
8. Do you wake up in the morning with headaches? (MH: Morning Headache)		
a) Never	b) Sometimes	c) Always
9. Do you constantly feel tired? (CF: Chronic Fatique)		
a) Never	b) Sometimes	c) Always
10. Do you have restlessness in sleep? (RS: Restless Sleep)		
a) Never	b) Sometimes	c) Always

Statistical Analysis

The data obtained in this study were analyzed with the SPSS v.20 program. Independent samples t-test, Mann

Whitney U test, Kruskal Wallis Variance analysis, Spearman's correlation rho efficient test and, Chi-square test were used. The results were interpreted at a significance level of 0.05. Power analysis was performed by G*Power 3.1.9.2 programme. Actual power was 0.80 (α error: 0.20, β error:0.80) (one tail) and calculated total sample size was 46 including 23 samples for Group 1 and 23 samples for Group 2. Actual power was 0.75 (α error: 0.25, β error:0.75) (two tails) and calculated total sample size was 54 including 27 samples for Group 1 and 27 samples for Group 2.

RESULTS

In the nasal septal deviation group, there were 18 males (52.9%) and 16 females (47.1%). In the control group, there were 11 males (40.7%) and 16 females (59.3%) (p=0.343, $\chi 2$=0.898). There were no significant differences between the ages of the groups (p>0.05) (Table 1). Mean body mass index (BMI) values of groups 1 and 2 were 24.57±4.04 kg/m2 and 24.29±4.14 kg/m2 respectively (p>0.05) (**Table 1**). Brinkmann Index values of the groups 1 and 2 were 2.50±5.36 and 1.03±2.80 respectively (p>0.05) (Table 1). Alcohol consumption was detected only in one participant in the control group. Mean mask usage time was 4.82±3.70 hours/day in the Septal deviation group and 6.03±3.33 hours/day in the control group (p>0.05) (**Table 1**).

In septal deviation group, deviation located was anterior deviation in 12 (35.3%) patients, posterior deviation in 13 (38.2%) patients and antero-posterior deviation in 9 (26.5%) patients. Right-sided deviation was detected in 15 (44.1%) patients and left-sided deviation was detected in 19 (55.9%) patients.

MSQ items and the total MSQ score of the septal deviation and control groups were presented in Table 1. Sleep Medications (SM) values of the deviation group (Group 1) (Mean rank= 28.50) were significantly lower than those in the control group (Group 2) (Mean rank= 34.15) (p<0.05). Morning Headache (MH) values of the deviation group (Group 1) (Mean rank= 27.60) were significantly lower than those in the control group (Group 2) (Mean rank= 35.28) (p<0.05). The other 8 MSQ items [Sleep Delay (SD), Sleep Awakenings (SA), Daytime Sleep (DS), Morning Fatigue (MF), Habitual Snoring (HS), Morning Awakening (MA), Chronic Fatigue (CF), Restless Sleep (RS)] and total MSQ scores were not different between the septal deviation and control groups (p>0.05) (**Table 1**).

In the septal deviation group, deviation location and MSQ items were shown in Table 2. There were no significant differences between MSQ items and total MSQ scores between the anterior, posterior and antero-posterior septal deviation groups (p>0.05) (**Table 2**).

Correlation Test Results in Septal Deviation Group

There were no significant correlations between MSQ items and total MSQ score; and facial mask usage time (hours), BMI, Brinkmann Index, Deviation side (right or left), or gender (p>0.05) (**Table 3**).

In older patients with septal deviation, Sleep Awakenings (SA), Habitual Snoring (HS), Morning Awakening (MA), and Total MSQ scores increased (p<0.05) (**Table 3**).

Table 1. MSQ items in the nasal septal deviation and control groups

	Group 1 (Nasal septal deviation) (n=34)			Group 2 (Control) (n=27)			P
	Mean	Median	Std.Dev.	Mean	Median	Std.Dev.	
Age*	32.23	28.50	11.34	27.59	26.00	7.57	0.073
BMI	24.57	23.80	4.04	24.29	23.78	4.14	0.788
Brinkmann index	2.50	0.00	5.36	1.03	0.00	2.80	0.341
Mask usage time (hours/ day)	4.82	3.00	3.70	6.03	6.00	3.33	0.139
MSQ items¶							
SD**	4.26	4.00	1.86	3.66	4.00	1.92	0.221
SA**	4.17	4.00	1.94	4.22	4.00	1.84	0.934
SM**	1.00	1.00	0.00	1.88	1.00	2.00	0.009
DS**	4.08	4.00	1.56	3.44	4.00	1.67	0.124
MF**	4.08	4.00	1.37	4.33	4.00	1.92	0.526
HS**	3.11	4.00	2.02	3.33	4.00	1.92	0.629
MA**	3.38	4.00	2.05	3.44	4.00	2.04	0.898
MH**	2.85	4.00	1.47	3.77	4.00	1.84	0.049
CF**	3.91	4.00	1.56	4.22	4.00	1.64	0.449
RS**	3.29	4.00	1.96	3.22	4.00	1.57	0.987
Total score*	33.70	32.50	9.01	34.88	37.00	10.71	0.641

*p value shows the results of Independent samples t-test, **p value shows the results of Mann Whitney U test, ¶SD: Sleep Delay, SA: Sleep Awakenings, SM: Sleep Medications, DS: Daytime Sleep, MF: Morning Fatigue, HS: Habitual Snoring, MA: Morning Awakening, MH: Morning Headache, CF: Chronic Fatigue, RS: Restless Sleep.

Table 2. In septal deviation group, deviation location and MSQ items

MSQ items¶	Group 1 (Anteriordeviation) (n=12)			Group 2 (Posteriordeviation) (n=13)			Group 3 (Antero-posteriordeviation) (n=9)			P*
	Mean	Median	Std.Dev.	Mean	Median	Std.Dev.	Mean	Median	Std.Dev.	
SD	4.00	4.00	1.27	4.46	4.00	2.06	4.33	4.00	2.34	0.782
SA	3.75	4.00	2.37	4.23	4.00	1.92	4.66	4.00	1.32	0.591
SM	1.00	1.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	1.000
DS	4.25	4.00	1.54	4.00	4.00	1.22	4.00	4.00	2.12	0.906
MF	4.25	4.00	0.86	3.76	4.00	1.48	4.33	4.00	1.80	0.566
HS	2.50	2.50	1.56	3.53	4.00	2.40	3.33	4.00	2.00	0.490
MA	2.75	2.50	2.00	3.30	4.00	2.17	4.33	4.00	1.80	0.197
MH	3.00	4.00	1.47	2.38	1.00	1.55	3.33	4.00	1.32	0.306
CF	4.25	4.00	1.54	3.53	4.00	1.66	4.00	4.00	1.50	0.512
RS	3.25	4.00	1.86	3.07	1.00	2.56	3.66	4.00	1.00	0.607
Total score	31.66	31.00	7.52	33.30	34.00	11.23	37.00	37.00	7.03	0.351

¶SD: Sleep Delay, SA: Sleep Awakenings, SM: Sleep Medications, DS: Daytime Sleep, MF: Morning Fatigue, HS: Habitual Snoring, MA: Morning Awakening, MH: Morning Headache, CF: Chronic Fatigue, RS: Restless Sleep. *p value shows the results of Kruskal Wallis Variance analysis

Table 3. Correlation test results in nasal septal deviation group*

		MSQ Items										Total MSQ Score
		SD	SA	SM**	DS	MF	HS	MA	MH	CF	RS	
Facial mask usage time (hours)	r	0.107	-0.074		-0.041	-0.027	-0.157	-0.180	0.044	0.091	0.019	-0.138
	p	0.548	0.678		0.818	0.879	0.376	0.308	0.806	0.608	0.917	0.438
Body mass index	r	0.012	0.237		-0.295	-0.150	0.136	0.114	0.083	0.181	-0.006	-0.015
	p	0.948	0.178		0.091	0.397	0.442	0.522	0.640	0.306	0.973	0.933
Brinkmann index	r	0.156	0.084		0.255	0.141	0.260	-0.112	0.133	0.190	0.226	0.110
	P	0.379	0.637		0.146	0.426	0.137	0.527	0.454	0.281	0.199	0.535
Deviation side (Code 1: Right sided SD, Code 0: Left sided SD)	r	0.077	-0.164		-0.051	0.334	-0.100	-0.156	-0.154	0.051	0.047	-0.055
	p	0.666	0.353		0.776	0.054	0.575	0.379	0.384	0.776	0.792	0.759
Age	r	0.107	0.404		-0.084	0.114	0.533	0.458	0.009	0.106	0.325	0.409
	p	0.547	0.018		0.638	0.521	0.001	0.006	0.959	0.550	0.060	0.016
Gender (Code 1: Male, Code 2: Female)	r	0.156	-0.082		0.291	0.072	-0.132	-0.059	0.014	0.050	-0.053	0.070
	p	0.378	0.646		0.095	0.684	0.456	0.739	0.936	0.777	0.764	0.696

*p value shows the results of Spearman's correlation rho efficient test, **All subjects in group 1 had 1.00 points for this item

DISCUSSION

Nasal obstruction is common in the population at a rate of 70-80% and septum deviation was detected incidentally as 40% in tomography scans (4). Many studies have shown that septum deviation has a negative effect on the quality of life and sleep quality (6-9). It is seen that the complaints of nasal obstruction increase with the use of masks in patients who apply to otolaryngology clinics (10).

In the present study, we investigated the effects of face mask usage on the sleep quality of patients with nasal septal deviation. Sleep quality was evaluated by MSQ (2).

Our results showed that Sleep Medications (SM) and Morning Headache (MH) values of the deviation group (Group 1) were significantly lower than those in the control group. There was no differences between other MSQ items and the total MSQ score of the septal deviation and control groups. We thought that surgical mask usage in the nasal septal deviation patients did not disturb sleep quality evaluated by MSQ.

In the nasal septal deviation group, the right-sided deviation was detected in 15 (44.1%) patients and left-sided deviation was detected in 19 (55.9%) patients. Deviation located was anterior deviation in 12 (35.3%) patients, posterior deviation in 13 (38.2%) patients and antero-posterior deviation in 9 (26.5%) patients. There were no significant differences between MSQ items and total MSQ scores between the anterior, posterior and antero-posterior septal deviation groups. We considered that deviation location did not affect the sleep quality of patients who used facial masks.

Correlation tests showed that there were no significant correlations between MSQ items and total MSQ score; facial mask usage time (hours), BMI, Brinkmann Index, Deviation side (right or left), or gender. However, in older patients with septal deviation, Sleep Awakenings (SA), Habitual Snoring (HS),, Morning Awakening (MA), and Total MSQ scores increased. It can be said that aging disturbed sleep quality of the septal deviation patients. Similarly, in the literature, it was reported that deviation of the septum and use of masks further affect sleep quality with increasing age (11).

In studies conducted in the literature, it was observed that the frequency of nasal blockage, mucosal crusting, nasal resistance, and nasal congestion increased with the rise in the duration of mask use (10). However, there are also studies showing that the use of masks can only increase nasal resistance and that compensatory mechanisms are activated and nasal flow is corrected (12).

According to the results of our study, daily mask usage did not cause any abnormalities in the MSQ scores of the group with septal deviation even though the fact that there are many types of these surgical masks and some masks do not have sufficient filtration features. As our nasal septal deviation patients' surgical mask usage did not disturb sleep quality, we thought that their surgical masks may have optimal filtration quality and did not increase nasal blockage and congestion.

In the literature (13,14), in the comparison of N95 masks and surgical masks; nasal blockage, mucociliary disorders, and postnasal discharge scores were observed more frequently in the use of N95 masks. In our study, we may not have seen these effects more clearly, since there were no patients using N95 masks routinely.

Obstructive sleep apnea (OSA) is one of the most common sleep disorders (15,16). Septum deviation is an anatomical disorder that contributes significantly to OSA. Since aging is a risk factor for the development of OSA (10), its prevalence is expected to increase with increasing life expectancy. OSA patients were not directly targeted in our study, but it should be noted that some of the nasal septal deviation patients are candidates for OSA patients in the future.

The fact that sleep medication scores are lower in patients with facial mask and septal deviation group is considered a paradox. However, it is known that these patients have lower sleep quality (17,18). In addition, since the need for sleep and daytime sleep is higher in this population, the transition to sleep is faster (19). Therefore, it was thought that they might need sleep medication less than the normal population. The use of drugs is not recommended in patients with obstructive sleep disorders, it has been observed that the use of hypnotic drugs-sleep medicaitons does not increase sleep quality and does not increase compliance with the use of positive pressure masks (20).

Limitations

The number of samples in our study can be considered as a limitation. However, the continuation of the pandemic and the fact that patients do not want to spend much time in hospitals and polyclinics limited the number of samples. Moreover, patients using N95 and other similar masks, which were used more at the beginning of the pandemic but whose use is gradually decreasing, could not be found and a comparison between the masks could not be made.

CONCLUSION

Facial mask usage did not cause sleep disorders in patients with nasal septal deviation. However, aging may cause disturbed sleep quality especially for the items of increased Sleep Awakenings (SA), Habitual Snoring (HS), Morning Awakening (MA), and Total MSQ scores in MSQ evaluation.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-interventional Researches Ethics Committee (Date: 09.12.2022, Decision No: 2021.12.17).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Kara M, Erdoğan H, Güçlü O, Sahin H, Dereköy FS. Evaluation of sleep quality in patients with nasal septal deviation via the Pittsburgh sleep quality index. J Craniofac Surg 2016; 27: 1738-40.
2. Zomer J, Peled R, Rubin AHE, Lavie P. Mini Sleep Questionnaire for screening large populations for excessive daytime sleepiness complaints. In: Koella EW, Ruther E, Schulz U (Eds). Sleep 84. Stuttgart, Gustav Fisher Verlag, 1985, pp 467-70.
3. Bayar Muluk N, Oğuztürk Ö, Arikan OK, Dikici O. Does sleep quality affect quality of lives of the workers exposed to occupational noise? Bidder Tıp Bilimleri Derg 2010; 2: 13-9
4. Uygur K, Tüz M, Dogru H. The correlation between septal deviation and concha bullosa. Otolaryngol Head Neck Surg 2003; 129: 33–6.
5. Sleep and Sleep Disorders. Centers for Disease Control and Prevention. (CDC-Accessed online at january 24, 2022).
6. Gulec TC, Yoruk O, Gulec M, et al. Benefits of submucous resection on sleep quality, daytime and dream anxiety in patients with nasal septal deviation. Sleep Biol Rhythms 2013; 11: 227–36.
7. Stewart MG, Smith TL, Weaver EM, et al. Outcomes after nasal septoplasty: results from the Nasal Obstruction Septoplasty Effectiveness (NOSE) study. Otolaryngol Head Neck Surg 2004; 130: 283–90.
8. Vural S, Tas E, Gursel AO. Evaluation of septoplasty patients with health status scale, rhinomanometry, and computed tomography. Kulak Burun Bogaz Ihtis Derg 2008; 18: 166–70.

9. Fidan T, Fidan V, Ak M, et al. Neuropsychiatric symptoms, quality of sleep and quality of life in patients diagnosed with nasal septal deviation. Kulak Burun Bogaz Ihtis Derg 2011; 21: 312–7.
10. Purushothaman PK, Priyangha E, Vaidhyswaran R. Effects of prolonged use of facemask on healthcare workers in tertiary care hospital during COVID-19 pandemic. Indian J Otolaryngol Head Neck Surg 2021; 73: 59–65.
11. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev 2017; 34: 70-81.
12. Monini S, Meliante PG, Salerno G, et al. The impact of surgical masks on the nasal function in the COVID-19 era. Acta Otolaryngol 2021; 141: 941-7.
13. Cengiz C, Can IH. The effect of N95 and surgical masks on mucociliary clearance function and sinonasal complaints. Eur Arch Otorhinolaryngol 2021: 1–6.
14. Sinkule EJ, Powell JB, Lee Goss F. Evaluation of N95 respirator use with a surgical mask cover: effects on breathing resistance and inhaled carbon dioxide. Ann Occup Hyg 2013; 57: 384-98.
15. Tobaldini E, Costantino G, Solbiati M, et al. Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. Neurosci Biobehav Rev 2017; 74: 321-9.
16. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014; 383: 736-47.
17. Lee KI, In SM, Kim JY, et al. Association of nasal septal deviation with the incidence of anxiety, depression, and migraine: A national population-based study. PLoS One 2021; 16: e0259468.
18. Cakir U, Sereflican M, Tuman TC, Yurttas V, Yildirim O, Oral M. Sleep and life quality of individuals with septum deviation. Psychiatry Clin Psychopharmacol 2016; 26: 88-188.
19. Dias PS, de Araujo-Melo MH, Neves DD, Lemes LN, Mosciaro MS, Bedoya S. Correlation between the oropharyngo-laryngoscopic findings and the severity of obstructive sleep apnea. Rev Col Bras Cir 2015; 42: 289-94.
20. Bradshaw DA, Ruff GA, Murphy DP. An oral hypnotic medication does not improve continuous positive airway pressure compliance in men with obstructive sleep apnea. Chest 2006; 130: 1369-76.

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Is the systemic immune-inflammation index a predictive marker of carotid artery stenosis?

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ABSTRACT

Introduction: The relationship between inflammation and atherosclerosis and ischemic stroke was shown in studies, and we aimed to evaluate the relationship between the systemic immune-inflammation (SII) index and carotid artery stenosis (CAS) in our study.

Material and Method: Forty patients with CAS with acute cerebrovascular disease and sixty three patients without CAS with acute cerebrovascular disease were included in the study. Demographic characteristics, neutrophil/lymphocyte ratio (NLR), and the SII indexes of the patients were compared between the groups with and without CAS.

Results: There was a statistically significant difference between the groups in terms of NLR and SII index values ($p<0.05$). In the ROC analysis, the sensitivity of the SII index was 65% and the specificity was 84.1%, based on a cut-off value of ≥14.032, and the sensitivity and specificity of NLR were 65% and 82.5%, repectively, based on a cut-off value ≥4.701. In terms of prognosis, poor outcome (mRS 3-6) was detected in 22/40 (55%) in the group with CAS, and a statistically significant difference was found between the groups ($p<0.05$). When evaluated in terms of mortality, the 1-month mortality rate in the group with CAS was 20% (8/40), and 4.8% (3/63) in the group without CAS ($p<0.05$).

Conclusion: In our study, the SII index and NLR were thought to be markers associated with the presence of CAS in patients with symptomatic CAS, and higher NLR and SII index values were found to be associated with poor prognosis and mortality.

Keywords: Carotid artery stenosis, inflammation, systemic immune-inflammation index (SII), neutrophil/lymphocyte ratio (NLR)

INTRODUCTION

Approximately 11.8% of all deaths in the world are due to stroke, and stroke ranks second after coronary artery diseases in terms of causing mortality (1). Carotid artery stenosis is one of the most important risk factors for ischemic stroke and is responsible for approximately 30% of strokes. The degree of carotid artery stenosis is correlated with the development of ischemic stroke, and the risk of stroke increases with stenosis of 50% or more in symptomatic patients and 70% or more in asymptomatic patients. (2).

Atherosclerosis is the most important factor in the formation of carotid artery stenosis (3). It is thought that chronic inflammation on the endothelial surface contributes to the process of the formation of atherosclerosis, and the increased risk of stroke in chronic inflammatory diseases supports this hypothesis. When studies on pathogenesis are examined, the presence of macrophages and T lymphocytes has been shown at every stage of the atherosclerotic process. Oxidative stress and inflammation lead to plaque destabilization in atherosclerosis, leading to the development of the thrombotic process. The expression of intercellular adhesion molecules by the endothelium in the area of atherosclerosis and the presence of activated T lymphocytes and macrophages in endarterectomy preparations support the contribution of the acute inflammatory response to the process. The fact that mediators released from symptomatic plaques, unlike asymptomatic plaques, cause rupture explains the risk of ischemic stroke in symptomatic stenosis and the contribution of inflammation to the process (4-6). Many previous studies have shown the relationship of inflammatory markers, especially C-reactive protein (CRP) and fibrinogen, with stable and unstable angina pectoris, peripheral artery disease, and carotid artery stenosis (7-9).

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CRP is one of the preferred acute-phase proteins in the follow-up of inflammation with acute phase response, and a strong correlation has been found between high CRP levels and risk of stroke and cardiovascular disease (10,11). It is reported as a result of 12 observational studies that CRP levels increase the risk of ischemic stroke (12,13).

In light of new developments, new diagnostic approaches focusing on the content of plaques rather than the known effects of the clinical consequences of atherosclerosis such as lumen narrowing, have been brought to the agenda. Recently, the obtained systemic immune inflammation (SII) index, which is used in combination with neutrophil, lymphocyte, and platelet counts as an inflammation marker and is considered to predict prognosis, has come to the fore. In studies, the SII index as an inflammation marker has been shown to have a stronger predictive value in showing inflammation than known parameters such as white blood cell (WBC) counts, the neutrophil/lymphocyte ratio (NLR), and neutrophil and lymphocyte counts (14-16).

No study has been found in the literature evaluating the relationship between the presence of carotid artery stenosis (CAS) and the SII index. It has been shown that inflammation is associated with atherosclerosis and ischemic stroke in different studies. We aimed to evaluate the relationship between the SII index and CAS.

MATERIAL AND METHOD

The study was carried out with the permission of KTO Karatay University, Faculty of Medicine Non-pharmaceutical and Non-medical Device Researches Ethics Committee (Date: 15.10.2021, Decision No: 2021/019). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This was a single-center, retrospective study. Forty patients with CAS and sixty three patients without CAS who were followed up in our clinic with the diagnosis of acute cerebrovascular disease between January 2019 and January 2021 were included in the study, and ultrasound of carotid and vertebral arteries was performed to these patients. Patients with a diagnosis of COVID-19, those who were pregnant, and patients with cancer, autoimmune disease, history of hematologic disease, history of immunosuppressive use, carotid dissection secondary to trauma, infectious process, or findings of sepsis (e.g. pneumonia, urinary system infections, pancreatitis, cholangitis) were excluded from the study. Ultrasound of carotid and vertebral arteries was performed in the first 5 days after symptom onset. CAS was evaluated using high-resolution B-mode carotid and vertebral artery Doppler ultrasonography. Accordingly, symptomatic patients with stenosis of a rate of ≥50% in the internal carotid artery (ICA) were considered to have significant stenosis. Patients without stenosis in the ICA were included in the comparison group. Demographic characteristics, chronic diseases, laboratory parameters, neutrophil/lymphocyte ratio, and the SII indexes of the patients were compared between groups with and without CAS.

Among the laboratory markers, WBC, neutrophil, lymphocyte and platelet counts, CRP, high-density lipoprotein (HDL), low-density lipoprotein (LDL), D-dimer, troponin, activated partial thromboplastin time (aPTT), prothrombin time (PT), and were recorded. Calculations were made according to the following formulae: NLR = neutrophil count/ lymphocyte count and SII index = neutrophil count x platelet count / lymphocyte count.

Ischemic stroke types were classified according to the Trial of Org 10 172 in Acute Stroke Treatment (TOAST) classification (17). Modified Rankin scale (mRS) scores at admission and 1 month, and National Institute of Health Stroke Scale (NIHSS) scores at admission were recorded in all patients. mRS 0-2 was considered a good prognosis and 3-6 as a poor prognosis. In addition, 30-day mortality was evaluated in all patients.

Demographic data, risk factors, laboratory findings, clinical findings, prognosis, and mortality findings were compared between the two groups.

Statistical Analysis

The data obtained in this study were analyzed using the IBM SPSS Statistics Version 21 package program.

The Shapiro-Wilk test was used because of the number of patients in the groups while investigating the normal distribution of the variables. While interpreting the results, 0.05 was used as the significance level; it was stated that in the case of $p<0.05$, the variables did not show normal distribution, and in the case of $p>0.05$, the variables showed normal distribution.

While examining the differences between the groups, the Mann-Whitney U test was used because the variables did not show normal distribution.

The Chi-square test was used while examining the relationships between groups of nominal variables.

While interpreting the results, 0.05 was used as the significance level, and it was stated that there was a significant relationship in case of $p<0.05$, and there was no significant relationship in case of $p>0.05$.

While interpreting the results, 0.05 was used as the significance level, and it was stated that there was a significant difference in case of $p<0.05$, and there was no significant difference in case of $p>0.05$.

Receiver operating characteristics (ROC) curve analysis was performed to determine the diagnostic values of some numerical measurements. Discrimination of the model was graded according to the area under the ROC curve as follows: 0.5-0.6 = weak discrimination, 0.6-0.7 = poor discrimination, 0.7-0.8 = acceptable discrimination, 0.8-0.9 = good discrimination, 0.9- 1 = excellent discrimination

RESULTS

Demographic Features

Forty patients with CAS and sixty three patients without CAS were included in the study. In the group with CAS, 18/40 (45%) of the patients were female and 22/40 (55%) were male. In the group without CAS, 25/63 (39.7%) of the patients were female, and 38/63 (60.3%) were male. The mean age was 73.15 years in the group with CAS and was 69.04 years in the group without CAS. There was no statistically significant difference between the groups in terms of age and sex (**Table 1**)

Table 1. Evaluation of the relationship between sex and age of the groups

	Groups				Total		p value
	CAS ≥50% (n=40)		Control (n=63)				
	n	%	n	%	n	%	
Sex							
Female	18	45	25	39.7	43	41.7	
Male	22	55	38	60.3	60	58.3	
Total	40	100	63	100	103	100	0.594
Age	**n**	**Mean**	**SD**	**Median**	**Min**	**Max**	
CAS ≥50%	40	73.15	12.98	75	37	93	
No CAS	63	69.04	11.35	70	38	92	
Total	80	70.64	12.11	71	37	93	0.072

SD: Standard Deviation. n: number of patients. p<0.05 Chi-square test was used for statistical analysis. Mann-Whitney U test was used for statistical analysis.

When the demographic data characteristics of the patients were examined, no statistically significant difference was found between the groups in terms of smoking, hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation (**Table 2**).

In the group with CAS, according to the NIHHS score, 3/40 (7.5%) had mild stroke, 16/40 (40%) had moderate stroke, and 21/40 (52.5%) had severe stroke. In group without CAS 18/63 (28.6%) had mild stroke, 29/63 (46%) had moderate stroke, and 16/63 (25.4%) had severe stroke.

When evaluated in terms of prognosis, poor outcomes (mRS 3-6) were found in 22/40 (55%) of the patients in the group with CAS, whereas it was found in 13/63 (20.6%) of the patients in the group without CAS. A statistically significant difference was found between the groups in terms of prognosis (p<0.05).

When evaluated in terms of mortality, the 1-month mortality rate was 20% (8/40) in the group with CAS, whereas it was 4.8% (3/63) in the group without CAS. Mortality was found to be statistically and significantly higher in the group with CAS (p<0.05) (**Table 2**).

According to the TOAST classification, the most common etiologic factor was large-artery atherosclerosis in 39/40 (97.5%) patients in the group with CAS. The most common etiologic factor was cardioembolism in 19/63 (30.2%) patients in the group without CAS (**Table 2**).

Table 2. Demographic and clinical features

	CAS ≥50% (n=40)	Control (n=63)	p value
	n (%)	n (%)	
Smoking			
Yes	6 (15%)	9 (14.3%)	0.920
No	34 (85%)	54 (85.7%)	
Hypertension			
Yes	21 (52.5%)	40 (63.5%)	0.269
No	19 (47.5%)	23 (36.5%)	
Diabetes mellitus			
Yes	13 (32.5%)	25 (39.7%)	0.462
No	27 (%67.5)	38 (60.3%)	
Hyperlipidemia			
Yes	13 (32.5%)	27 (42.9%)	0.293
No	27 (67.5%)	36 (57.1%)	
Prior ischemic stroke			
Yes	5 (12.5%)	6 (9.5%)	0.634
No	35 (87.5%)	57 (90.5%)	
Atrial fibrillation			
Yes	11 (27.5%)	26 (41.3%)	0.156
No	29 (72.5%)	37 (58.7%)	
Mortality			
Yes	8 (20%)	3 (4.8%)	0.015
No	32 (80%)	60 (95.2%)	
NIHSS			
Mild	3 (7.5%)	18 (28.6%)	
Modatere	16 (40%)	29 (46%)	0.005
Severe	21 (52.5%)	16 (25.4%)	
TOAST			
Large-artery atherosclerosis	39 (97.5%)	13 (20.69%)	
Cardioembolism	1 (2.5%)	19 (30.2%)	
Small-vessel occlusion	0 (0%)	13 (20.6%)	<0.001
Stroke of other determined etiology	0 (0%)	2 (3.2%)	
Stroke of undetermined etiology	0 (0%)	16 (25.4%)	
MRS			
Good (MRS 0-2)	18 (45%)	50 (79.4%)	<0.001
Poor (MRS 3-6)	22 (55%)	13 (20.6%)	

n: number of patients, Chi-square test was used for statistical analysis. p<0.05 shows a statistical difference. TOAST: Trial of Org 10172 in acute stroke. NIHSS: National Institutes of Health Stroke Scale.MRS: Modified Rankin Scale

Laboratory findings

When laboratory parameters were compared between the two groups, there was a statistically significant difference in terms of WBC and monocyte counts, CRP, D-dimer, troponin, PT, aPTT, LDH, and HDL.

The mean neutrophil count was statistically significantly higher in the group with CAS (7.86±2.54 x103/μL) compared with the group without CAS (6.14±2.4 x103/μL) (p<0.05). The mean lymphocyte count was statistically significantly lower in the group with CAS (1.58±0.7 x103/μL) compared with the group without CAS (2.4±0.94 x103/μL) (p<0.05).

The mean value of platelet count was statistically significantly higher in the group with CAS (293.82±65.66 x103/μL) compared with the group without CAS (239.82±68.45 x103/μL). (p<0.05) (**Table 3**).

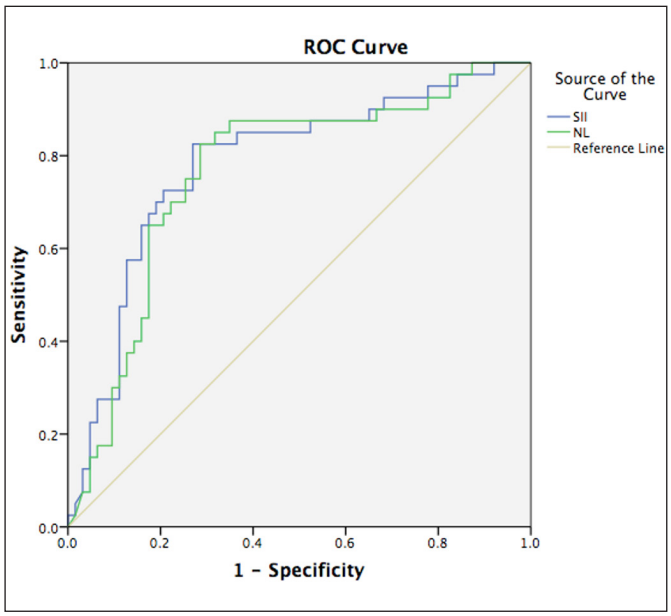

Figure 1. The ROC analysis curve

There was a statistically significant difference between the groups in terms of NLR and SII index (p<0.05) (**Table 4**).

ROC analysis was performed for the SII index and NLR. For the SII index, the sensitivity was 65% and specificity was 84.1% based on the cut-off value ≥14.032, and the sensitivity was 65% and specificity was 82.5% based on the NLR cut-off value ≥4.701. Details of the ROC analysis are given in **Table 5** and **Figure 1**.

Table 3. Comparison of Laboratory Parameters Between Groups with and without CAS

	CAS ≥50% (n=40)	Control (n=63)	
	Mean ± SD (min-max) (median)	Mean ± SD (min-max) (median)	p value
White Blood Cell, ×10³/μL	10.3±2.95 (5.88-16) (10.8)	9.63±2.99 (4.8-18.8) (8.9)	0.267
Neutrophil, ×10³/μL	7.86±2.54 (3.7-13.6) (7.15)	6.4±2.4 (2.7-13.3) (5.7)	0.001
Lymphocyte, ×10³/μL	1.58±0.7 (0.34-2.97) (13.6)	2.4±0.94 (0.34-3.9) (2.5)	<0.001
Monocyte, ×10³/μL	0.71±0.46 (0.2-3.2) (0.67)	0.72±0.34 (0.2-2.8) (0.7)	0.571
Platelet, ×10³/μL	293.82±65.66 (169-402) (299)	239.82±68.45 (3.18-396) (238)	<0.001
C reactive protein (CRP) mg/L	21.28±29.52 (1.7-108) (7.45)	11.69±24.66 (0.6-190) (5.28)	0.080
D-Dimer, ng/mL	2.45±2.49 (0.1-11.1) (1.8)	2.85±2.63 (0.1-12.1) (2)	0.405
Troponin, ng/mL	21.19±37.49 (2-229) (8.45)	35.38±137.43 (0.1-850) (6.8)	0.097
Prothrombin time (PT) s	12.65±3.68 (8.88-31.2) (11.8)	12.46±4.1 (8.58-38.9) (12)	0.743
Activated Partial thromboplastin time (aPTT) s	26.92±5.67 (19.3-42.3) (26.45)	26.93±7.54 (16.5-55.4) (26.5)	0.636
Lactate dehydrogenase (LDL) U/L	122.15±44.25 (13-263) (124)	139.3±62.4 (13-400) (124)	0.285
High density lipoprotein (HDL) U/L	39.53±11.03 (11-61)(41)	42.76±11.53 (1-72) (43)	0.116

SD: Standard Deviation, n: number of patients. Mann-Whitney U test was used for statistical analysis. P<0.05 shows the statistical difference.

Table 4. Comparison of Neutrophil/Lymphocyte ratio and SII index between groups

	n	Mean	SS	Medyan	Min	Max	p-value
Neutrophil/Lymphocyte							<0.001
CAS ≥50%	40	6.61	5.9	5.17	1.58	36.47	
Control	63	3.84	5.03	2.19	0.9	36.47	
Total	80	4.92	5.53	3.27	0.9	36.47	
SII index							<0.001
CAS ≥50	40	2021.14	1786.12	1712.02	267.44	10102.35	
Control	63	940.29	1224.07	535.38	14.92	8169.41	
Total	80	1360.04	1552.66	770.92	14.92	10102.35	

SD: Standard Deviation, n: number of patients, Mann-Whitney U test was used for statistical analysis. p<0.05 shows a statistical difference. SII: Systemic immune inflammation index.

Table 5. ROC curve analysis results for significant laboratory variables.

	AUC	SD	p-value	95% CI		Cut-off	Sensitivity	Specificity
				Lower	Upper			
SII index	0.782	0.48	<0.001	0.688	0.877	≥14.032	65	84.1
NLR	0.765	0.50	<0.001	0.668	0.862	≥4.701	65	82.5

SD: Standard Deviation, AUC: Area Under the Curve. ROC analysis was used for statistical analysis. SII index: Systemic immune inflammation index. NL: Neutrophil/Lymphocyte.

DISCUSSION

The SII index is a marker that has recently been investigated concerning prognosis and the inflammatory process. In our study, a statistically significant increase was found between symptomatic CAS, the SII index, and NLR when patients with and without CAS as the etiologic factor followed up during the cerebrovascular disease process were compared.

Studies evaluating the relationship between the SII index and related CAS concluded that the SII index was a parameter that could predict severe obstruction hemodynamically and was a predictor of major cardiac risk events that might develop in patients with coronary artery disease (18,19). We could not find a similar study in the literature, so, based on this hypothesis, we evaluated patients with acute ischemic stroke with symptomatic CAS, and we thought that CAS was associated with the SII index and NLR.

When ischemic cerebrovascular disease develops, neutrophil levels increase and lymphocyte levels decrease in case of acute stress, and this situation has been found to be associated with the severity of ischemia. Lymphopenia develops due to the apoptosis of lymphocytes under the influence of physiologic stress during the inflammation process (16). In addition, an increase in the neutrophil count causes atherosclerosis by causing plaque rupture, reperfusion damage, and plaque remodeling, which plays a critical role in the development of CAS. Increased neutrophil levels increase platelet levels and cause platelet aggregation. In addition, neutrophils also stimulate thrombogenesis by affecting tissue factors. Thus, besides the increase in neutrophils, the correlated increase in platelets leads to inflammation and thrombosis. Activated platelets cause the rupture of thrombus formation from atherosclerotic plaques and increase the risk of rupture by activating the release of proteolytic enzymes and myeloperoxidase-like oxidation enzymes in activated neutrophils. Ultimately, ruptured plaque formation leads to ischemic stroke. An increase in neutrophil levels in the histopathologic examinations of ruptured plaques that cause ischemic stroke or stenosis supports this situation. Nasr et al. (20) reported that the development of cerebral ischemia secondary to symptomatic CAS was associated with neutrophil levels. In our study, when the laboratory parameters of the groups with and without CAS were compared, the increase in neutrophil and platelet levels and a decrease in lymphocyte levels were considered statistically significant. The SII index, which evaluates all these neutrophil, lymphocyte, and platelet levels together, has been shown to be more valuable in predicting prognosis compared with other inflammatory markers (16).

In our study, when we compared the patients with and without CAS as the etiologic factor followed up during the cerebrovascular disease process, a statistically significant correlation was found with NLR, as well as the SII index, in patients with symptomatic CAS.

Supporting the results of our study, another study evaluated NLR in patients with CAS and it was reported that the NLR was increased in these patients, showing the risk of rupture in non-calcified carotid artery plaques (21). It has been shown in previous studies that NLR is a marker of poor prognosis in ischemic stroke (22). In our study, similarly, mortality was found to be statistically significantly higher in patients with symptomatic CAS.

In a review that evaluated the findings of 18 studies examining the prognostic value of NLR and PLR in patients with CAS, NLR was found to be associated with carotid intima-media thickness, carotid plaques, carotid stenosis, symptomatic stenosis, post-stenting re-stenosis, and cognitive dysfunction after CAS. It has been emphasized that NLR has prognostic value in evaluating the progression of atherosclerosis in subclinical atherosclerosis and carotid artery disease and that it can be used in patient management and individual treatment (23).

We found a study in which the clinical benefit and utility of the SII index were evaluated in 165 patients who underwent intravenous thrombolytic therapy for acute cerebrovascular disease when we look at the studies in which the SII index and NLR were evaluated together. For NLR, ROC-AUC was 0.86, sensitivity was 71.3%, and specificity was 65.7%. For the SII index, ROC-AUC was 0.802, sensitivity was 58.7%, and specificity was 72.7%. As a result, it was concluded that the SII index and NLR provided moderate benefit in predicting the risk of bleeding that might occur following thrombolytic therapy (24). Similarly, it was emphasized that the SII index was a marker that predicted hemorrhagic transformation in patients who had a stroke due to large artery atherosclerosis of anterior circulation (25). In our study, in the ROC analysis of patients with symptomatic CAS, the sensitivity of the SII index was 65% and the specificity was 84.1% based on the cut-off value ≥14.032. The sensitivity of NLR was found to be 65% and specificity 82.5%, based on the cut-off value ≥4.701.

To evaluate the prognostic role of the SII index and NLR in patients with acute ischemic stroke, in another study involving 277 patients, the mRS scores of the patients were recorded at the 1st, 3rd, 6th, and 12th months. Multivariate analysis revealed that the initial NLR had a prognostic role at 3 months after ischemic stroke (26). Considering the relationship between the SII index and disease severity in patients with acute ischemic stroke,

it was reported that the SII index was an independent risk factor in showing the severity of stroke in a study of 362 patients (27). In our study, mortality was higher in the patient group with symptomatic CAS than in the other group without CAS. In addition, in the group with symptomatic CAS, the rate of poor outcomes according to mRS was higher in the 1-month follow-up.

In addition to the relationship of the SII index with atherosclerotic and inflammatory processes, its relationship with prognosis has been mentioned in various studies. In the first of these, 270 patients who had sinus vein thrombosis were followed up for an average of 22 (range, 6-66) months, and the prognostic value of the SII index was examined. It was reported to be a potential predictor of poor prognosis (28). The SII index was used for the first time as a marker to evaluate the relationship between cancer and inflammation, and it was found as a predictor of poor prognosis in solid tumors such as hepatocellular carcinoma and colorectal cancer (29-31).

Given that our study was a retrospective study, we could not make a long-term follow-up and evaluate the prognosis, which was one of the limitations of our study. Other limitations of our study were that it was a single-center study and that the number of patients was low. We think that our findings will be supported by prospective multicenter studies with a larger patient samples on the effectiveness of the SII index by comparing it with other inflammatory markers.

CONCLUSION

In our study, the SII index and NLR were thought to be markers associated with the presence of symptomatic CAS, and high NLR and SII indexes were found to be associated with poor prognosis and mortality. We think that prospective randomised controlled studies with a larger number of patients evaluating the relationship of the SII index to acute ischemic stroke and CAS are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KTO Karatay University, Faculty of Medicine Non-pharmaceutical and Non-medical Device Researches Ethics Committee (Date: 15.10.2021, Decision No: 2021/019).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Feigin VL, Krishnamurthi RV, Parmar P, et al. Update on teh Global Burden of ischemic and Hemorrhagic Stroek in 1990-2013 The GBD 2013 Study. Neuroepidomiology 2015; 45: 161-76.
2. Liapis CD, Bell PR, Mikhailidis D, et al, ESVS Guidelines Collaborators. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg 2009; 37: 1-19.
3. Flaherty ML,Kissela B, Khoury JC et al. Carotid artery stenosis as a cause of stroke. Neuroepidomyology 2013; 40: 36-41.
4. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. Athero Gene Investigators. Impact of infectious burden on extent and long-term prognosis of atherosclerosis. Circulation 2002; 105: 15-21.
5. Utku U, Çelik Y.İnmede etyoloji sınıflandırma ve risk faktörleri Serebrovasküler Hastalıklar Güneş Tıp Yayınevi 2009 S: 51-62.
6. Boehme AK, Esenwa C, Elkind MS. Stroke Risk Factors, Genetics, and Prevention.Circ Res 2017; 120: 472-95.
7. Jander S, Sitzer M, Schumann R, et al. Inflammation in high-grade carotid stenosis: a possible role for macrophages and T cells in plaque destabilization. Stroke 1998; 29: 1625-30.
8. Anderson JL, Carlquist JF, Muhlestein JB, Horne BD, Elmer SP. Evaluation of C-reactive protein, an inflammatory marker, and infectious serology as risk factors for coronary artery disease and myocardial infarction. J Am Coll Cardiol 1998; 32: 35-41.
9. Darbousset R, Thomas GM, Mezouar S, et al. Tissue factor-positive neutrophils bind to injured endothelial wall and initiate thrombus formation. Blood 2012; 120: 2133-43.
10. Arvin B, Neville LF, Barone FC, Feuerstein GZ. The rol of inflamation and cytokines in brain injury. Neurosci Biobehav Rev 1996: 20: 445-52.
11. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women . N Engl J Med 2000; 342: 836-43.
12. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010; 375: 132-40.
13. Zhou Y, Han W, Gong D, Man C, Fan Y. Hs-crp in stroke: a meta-analysis. Clinica Chimica Acta; Int J Clin Chem 2016; 453: 21–7.
14. Wang L, Song Q, Wang C et al. Neutrophil to lymphocyte ratio predicts poor outcomes after acute ischemic stroke: A cohort study and systematic review. J Neurol Sci 2019; 406: 116445.
15. Fest J, Ruiter R, Ikram MA, Voortman T, van Eijck CHJ, Stricker BH. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. Sci Rep 2018; 8: 10566.
16. Yi HJ, Sung JH, Lee DH. Systemic inflammation response index and systemic immune-inflammation index are associated with clinical outcomes in patients treated with mechanical thrombectomy for large artery occlusion. World Neurosurg 2021; 153: e282-e289.
17. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24: 35-41.

18. Erdoğan M, Erdöl MA, Öztürk S, Durmaz T. Systemic immune-inflammation index is a novel marker to predict functionally significant coronary artery stenosis. Biomark Med 2020; 14: 1553-61.
19. Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest 2020; 50: e13230.
20. Nasr N, Ruidavets JB, Arnal JF, Sie P, Larrue V. Association of neutrophil count with microembolization in patients with symptomatic carotid artery stenosis. Atherosclerosis 2009; 207: 519-23.
21. Yüksel İÖ, Köklü E, Arslan Ş, et al.Association of neutrophil/lymphocyte ratio with plaque morphology in patients with asymptomatic intermediate carotid artery stenosis. Korean Circ J 2016; 46: 699-705.
22. Köklü E, Yüksel İÖ, Arslan Ş, et al. Is elevated neutrophil-to-lymphocyte ratio a predictor of stroke in patients with intermediate carotid artery stenosis? J Stroke Cerebrovasc Dis 2016; 25: 578-84.
23. Pereira-Neves A, Fragão-Marques M, Rocha-Neves J, et al. The impact of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratıo in carotıd artery dısease. Rev Port Cir Cardiotorac Vasc 2021; 28: 45-51.
24. Topcuoglu MA, Pektezel MY, Yilmaz E, Arsava EM. Systemic inflammation indices in patients with acute ischemic stroke treated with intravenous tissue plasminogen activator: clinical yield and utility. Angiology 2021; 72: 279-284.
25. Yang Y, Han Y, Sun W, Zhang Y. Increased systemic immune-inflammation index predicts hemorrhagic transformation in anterior circulation acute ischemic stroke due to large-artery atherosclerotic. Int J Neurosci 2021: 1-7.
26. Li LH, Chen CT, Chang YC, Chen YJ, Lee IH, How CK. Prognostic role of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune inflammation index in acute ischemic stroke: A STROBE-compliant retrospective study. Medicine (Baltimore) 2021; 100: e26354.
27. Hou D, Wang C, Luo Y, et al.Systemic immune-inflammation index (SII) but not platelet-albumin-bilirubin (PALBI) grade is associated with severity of acute ischemic stroke (AIS). Int J Neurosci 2020: 1-6.
28. Li S, Liu K, Gao Y et al. Prognostic value of systemic immune-inflammation index in acute/subacute patients with cerebral venous sinus thrombosis. Stroke Vasc Neurol 2020; 5: 368-73.
29. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget 2017; 8: 75381-8.
30. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014; 20: 6212-22.
31. Passardi A, Scarpi E, Cavanna L, et al. Inflammatory indexes as predictors of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer. Oncotarget 2016; 7: 33210-9.

Original Article

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Forensic-medical retrospective analysis of cardiovascular injuries admitted to the emergency department

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ABSTRACT

Aim: Vascular and cardiac injuries are rare cases compared to other traumas in terms of admission rates to emergency services. Vascular emergencies secondary to trauma are among 1-2.5% of all trauma patients admitted to the emergency department. In addition, the admission rate of heart injuries is around 1%. With this study, we will analyze and interpret cardio-vascular injuries, which are rare compared to other traumas, from a forensic-medical aspect.

Material and Method: This study is a retrospective cohort study using data from our hospital's automation and archive system. Patients who developed iatrogenic trauma, had solid organ injury in addition to their existing injury, were brought to the emergency room as deceased, and patients who came to the emergency room with cardio-pulmonary resuscitation were not included in the study. A total of 411 cases, 88 cardiac injuries and 323 vascular injuries, aged 16-82 years were included in the study.

Results: In the 5-year analysis, the rate of life-threatening injuries due to cardiac and vascular injuries among cardiovascular emergencies is 22%. 88 patients with cardiac injury were included in this study.18 (20.5%) of the patients were female and 70 (79.5%) were male. The most common injury sites were upper extremity (43.7%), lower extremity (25.7%), thorax (21.4%), abdomen-pelvic region (4.1%), head-neck (2.6%), multiple vascular injury (2.1%), respectively.

Conclusion: Cardiovascular injuries are among the traumas with high mortality and morbidity. It is important that the cases consulted to cardiovascular surgery in the emergency department are forensic cases and that the forensic reports of these cases are carefully prepared.

Keywords: Cardiac injury, vascular injury, emergency department, forensic medicine

INTRODUCTION

All cases that occur due to traffic accidents, assault, force, explosive and firearm injuries, injuries with various tools and similar actions of people or reasons for which they are responsible are in the nature of forensic cases (1,2). Vascular emergencies secondary to trauma are among 1-2.5% of all trauma patients admitted to the emergency department (3,4). Although vascular injuries are less common than other trauma cases, the risk of developing morbidity and mortality is high if intervention is delayed. If the medicotechnical structure of the center applied with vascular trauma is weak or there is little experience in approaching vascular emergencies, mortality rates can reach up to 25%. In addition, if it is taken into account that vascular injuries can be accompanied by additional damage such as nerve and muscle injury or loss of limb, especially in relation to the extremity, it will be better understood how high the morbidity of vascular traumas is (5-7).

Cardiac injuries have a relatively low rate of admission to emergency services compared to vascular traumas. The clinical course of cardiac injuries tends to worsen rapidly. Cardiac tamponade, shock and death due to trauma occur before the patient arrives at the hospital. The rate of reaching the hospital is around 6% of patients with cardiac injury. Those who can reach the hospital have only a 50% chance of survival (8,9). As can be seen, early intervention is very important in patients presenting with both cardiac and vascular injuries. Regarding these patients, diagnosis and treatment protocols should be clearly defined, and health institutions should always be prepared to meet this particular patient group. Cardio-vascular traumas are etiologically blunt, penetrating

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and iatrogenic. Because iatrogenic injuries occur in healthcare settings, they may not be considered a true traumatic injury. Since blunt or penetrating injuries are in the category of both emergency and forensic cases, they are cases that should be approached sensitively from a medico-legal perspective. With this study, we will analyze the last 5 years of cardiovascular injuries admitted to Bursa Yüksek İhtisas Training and Research Hospital Emergency Department. In this way, we aim to share the experience of our cardiovascular surgery clinic in terms of approach to cardiovascular emergencies and to evaluate this special patient group from a forensic perspective.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.01.2022, Decision No: 2011-KAEK-25 2022/02-26). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study is a retrospective cohort study using data from our hospital's automation and archive system. The requirement for written informed consent was waived. In this study, which was planned as a single center, cardiac and vascular injury cases who applied to the emergency department of Bursa Yüksek İhtisas Training and Research Hospital between 01.01.2017 and 01.01.2022 and were consulted to our cardiovascular surgery clinic were examined. Those who applicated arterial or venous catheters, those who develop injury during cardiac catheterization, iatrogenic traumas, patients with solid organ injury in addition to their current injury, patients who were brought to the emergency room as dead and those who came to the emergency room with cardiopulmonary resuscitation were excluded from the study. A total of 411 cases, 88 cardiac injuries and 323 vascular injuries, aged 18-82 years were included in the study. These 411 cases constitute approximately 22% of the total 1868 consultations requested from our clinic by the emergency department clinic within the specified date range.

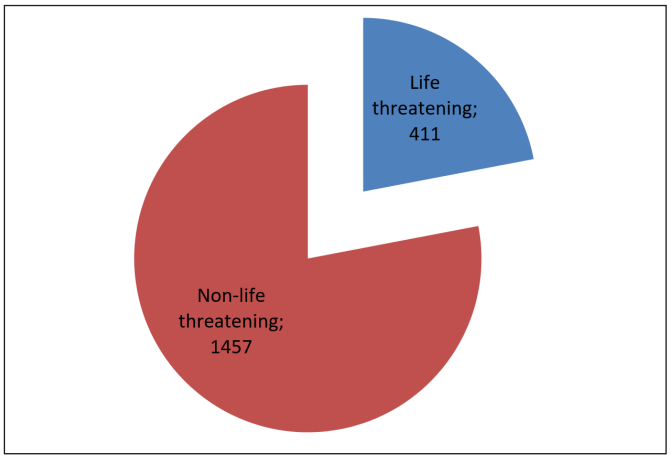
The patients were handled separately as cardiac injuries and vascular injuries at the time of admission. Each group was divided into two groups, survivor and non-survivor, and analyzed by considering parameters such as gender and injury type. In addition, separate analyzes were performed according to the site of injury and the injured vessel. Etiologically, the data were interpreted by grouping such as those who developed penetrating and blunt trauma, those who survived and those who developed death.

RESULTS

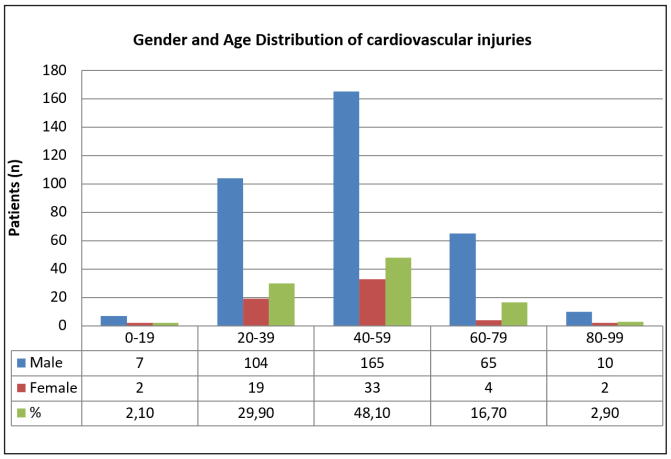
In the 5-year analysis, the rate of life-threatening injuries due to cardiac and vascular injuries among cardiovascular emergencies is 22%. (**Graph 1**) 88 patients with cardiac injury were included in this study. 18 (20.5%) of the patients were female and 70 (79.5%) were male. Those who did not develop in-hospital mortality were included in survivors group (n = 60, 68.2%) and those who did were included in non-survivors group (n = 28, 31.8%). In the non-survivors group, there were 12 patients (13.6%) with stab wounds and 16 patients (18.1%) with gunshot wounds. Of the 411 patients presenting with cardio-vascular injury, there were 60 (14.5%) female and 351 (85.4%) male patients. Of 39 (9.4%) patients in the non-survivor group, 31 (7.5%) were male and 8 (1.9%) were female (**Table 1**). The age range of the patients admitted to the emergency department due to cardio-vascular injury was 16-88 years. The mean age was 43.4±11.1 years (**Graph 2**).

Table 1. Analysis of patients presenting with cardiovascular injury

Cardiac injuries	**Survivor (n=60)**		**Non-survivor (n=28)**
Male/Female (n,%)	48 (54.5%) / 12 (13.6%)		22 (25%) / 6 (6.8%)
Stab wounds (n,%)	40 (45.4)		12 (13.6%)
Gunshot woundt (n,%)	17 (19.3%)		16 (18.1%)
Blunt trauma (n,%)	3 (3.4%)		-
Vascular injuries	**Survivor (n=312)**		**Non-survivor (n=11)**
Male/Female (n,%)	272(84.2%) / 40(12.3%)		9 (2.7%) /2 (0.6%)
Stab wounds (n,%)	175 (54.1%)		6 (1.8%)
Gunshot woundt (n,%)	127 (39.3%)		4 (1.2%)
Blunt trauma (n,%)	10 (3%)		1 (0.3%)
Total	**Survivor (n=372) (90.5%)**	**Non-survivor (n=39) (9.4%)**	**Total**
Male/Female (n,%)	320 (77.8%) / 52(12.6%)	31 (7.5%) / 8 (1.9%)	351(85.4%)/60(14.5%)
Stab wounds (n,%)	215 (52.3%)	18 (4.3%)	233(56.6%)
Gunshot woundt (n,%)	144 (35%)	20 (4.8%)	164 (39.9%)
Blunt trauma (n,%)	13 (3.1%)	1 (0.2%)	14 (3.3%)



Graphic 1. Cardiovascular life-threatening rate among patients consulted from the emergency department



Graphic 2. Age-gender distribution of patients presenting with cardiovascular injury

The most common injury sites were upper extremity (43.7%), lower extremity (25.7%), thorax (21.4%), abdomen-pelvic region (4.1%), head-neck (2.6%), multiple vascular injury (2.1%), respectively (**Table 2**). According to the frequency of the injured vessels, the most common injury was seen in the radial (18.8%) and ulnar (13.3%) arteries, while the least injured vessel was the iliac vein (0.9%) (**Table 3**).

Table 2. Analysis of patients by injury site

Site of injury	Survivors (n=372)	Non-survivors (n=39)
Head-neck (n,%)	10 (2.4%)	1 (0.2%)
Thorax (n,%)	60 (14.5%)	28 (6.8%)
Abdominal and pelvic region (n,%)	14 (3.4%)	3 (0.7%)
Upper extremity (n,%)	179 (43.5%)	1 (0.2%)
Lower extremity (n,%)	102 (24.8%)	4 (0.9%)
Multiple* (n,%)	7 (1.7%)	2 (0.4%)

* Multiple vascular injuries are 4 lower extremity + upper extremity, 4 abdominal-pelvic region + lower extremity, 1 head-neck + lower extremity injuries.

Table 3. Survival data by anatomical location of vascular injury

	Survivor (N=312)	Non-survivor (N=11)
Femoral artery	47	2
Femoral vein	15	2
Popliteal artery	18	-
Popliteal vein	6	-
Anterior tibial artery	9	-
Posterior tibial artery	7	-
Abdominal aorta	5	1
Inferior vena cava	3	1
Iliac artery	4	-
Iliac vein	2	1
Carotid artery	7	1
Jugular vein	3	-
Axillary artery	5	1
Subclavian vein	8	-
Brachial artery	31	-
Ulnar artery	43	-
Radial artery	61	-
Brachial vein	9	-
Cephalic vein	22	-
Multiple vascular injury	7	2

DISCUSSION

Cardiovascular injuries are among the few traumas encountered in emergency departments due to trauma. The rate of vascular injuries among all traumatic injuries is 3%, whereas cardiac injuries are only 1% (10,11). Despite these low rates, the mortality risk due to cardiac trauma among thoracic traumas is around 40%. In this descriptive study, we analyzed a small number of cardiovascular traumas with a high risk of morbidity and mortality. In the light of the data obtained, we shared our 5-year cardio-vascular injury experience of our clinic and our forensic findings for this patient group.

In our study, it was determined that the injuries in 22% of the emergency cases consulted by the cardiovascular surgery clinic by the emergency department were of a nature that would endanger the life of the person. In the study of Altun et al. (12), this rate was found to be 35%, which is in line with our study. Also, patients who applied to the emergency department due to cardiovascular injury were between the ages of 16-82 and the mean age was 43.4±11.1 years. In a study reported by Altundağ et al. (13), the cases evaluated due to cardiovascular injury range from 11 to 88 years of age. The mean age of the patients is 41.2±15.9 years. Our study is similar to this study in terms of age distribution and mean age. In our study, the male sex ratio was 85.4% (351/411) among the patients evaluated for cardiovascular injury. This rate is similar to the majority of studies conducted in our country. Many studies show that the majority of forensic cases receiving service from emergency services are men. In our country, it is seen that men are exposed to forensic injuries related to cardiovascular surgery at a much higher rate than women (14-17).

According to our study, the majority of injuries (56.6%) were caused by stab wounds, and the second most common cause of injury was gunshot wounds (39.9%). In another study parallel to our study, the most common cause of injuries was stab wounds with a rate of 43%, while

the second most common cause was gunshot wounds (18). Also, the thoracic region was found to be the most common location in fatal injuries with a rate of 6.8%, according to the site of injury. When evaluated in terms of cardiac injury, it is seen that the mortality rate among cardiac injuries is 31.8%. Studies have reported that this rate reaches up to 80% (10). Mortality data similar to ours were reported in the study of Manduz et al. (19). In the death series due to cardiac injuries performed by Uluçay et al. (13) between 2010-2012; It was reported that 3/4 of the cases died at the scene, and in the study conducted in İzmir, the majority of the cases (69.3%) died at the scene (18).

In our study, the most frequently injured place was the upper extremity in injuries that did not result in death, while the most frequently injured place was the thoracic region in cases that resulted in death. In the meta-analysis reported by Prichayudh et al. (20), it is seen that there are similar results in terms of injury site and frequency. It is possible to reduce mortality with early and appropriate intervention in extremity injuries. Despite intervention in the thoracic region, heart and great vessel injuries, the risk of mortality remains high. In conclusion, cardiovascular injuries are injuries with a high risk of mortality and morbidity depending on the location of the injury. It is obvious that the risk of mortality will decrease if an effective intervention is made at the right time for this particular patient group. For this, pre-hospital care services should be improved as well as increasing the efficiency of in-hospital services.

The most important limitations of our study are that it is single-centered, retrospective, and the number of patients is low. More comprehensive publications with larger numbers of patients are needed to support existing data.

CONCLUSION

Cardiovascular injuries are among the traumas with high mortality and morbidity. If these injuries are intervened early and effectively, serious reductions in mortality risks will be achieved. It is important that the cases consulted to cardiovascular surgery in the emergency department are forensic cases and that the forensic reports of these cases are carefully prepared. It should not be forgotten that it may cause physician liability, especially in cases where cases result in mortality, in cases where it is forgotten to notify the judicial authorities.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.01.2022, Decision No: 2011-KAEK-25 2022/02-26).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Fincancı SK. Adli olguya yaklaşım. Yeni yasalar çerçevesinde hekimlerin hukuki ve cezai sorumluluğu. Tıbbi Malpraktis ve Adli Raporların Düzenlenmesi Sempozyum Dizisi. Şubat 2006; 48: 92-103.
2. Sever M, Ulaş ES, Koşargelir M. Bir üçüncü basamak hastane acil servisine başvuran adli nitelikli çocuk hastaların değerlendirilmesi. Ulus Travma Acil Cerrahi Derg 2010; 16: 260-7.
3. Sugrue M, Caldwell EM, Damours SK, Crozier JA, Deane SA. Vascular injury in Australia. Surg Clin North Am 2002; 82: 211e9.
4. Caps MT. The epidemiology of vascular trauma. Semin Vasc Surg 1998; 11: 227e31.
5. Loh SA, Rockman CB, Chung C, et al. Existing trauma and critical care scoring systems underestimate mortality among vascular trauma patients. J Vasc Surg 2011; 53: 359-66.
6. Perkins ZB, De'Ath HD, Aylwin C, Brohi K, Walsh M, Tai NRM. Epidemiology and outcome of vascular trauma at a British Major Trauma Centre. Eur J Vasc Endovasc Surg 2012; 44: 203-9.
7. VanWaes OJ, Navsaria PH, Verschuren RC, et al. Management of penetrating injuries of the upper extremities. Ulus Travma Acil Cerrahi Derg 2013; 19: 405-10.
8. Campbell NC, Thomson SR, Muckart DJ, Meumann CM, Van Middelkoop I, Botha JB. Review of 1198 cases of penetrating cardiac trauma. Br J Surg 1997; 84: 1737-40.
9. Akay T. Kalp ve damar yaralanmaları. Toraks Cerrahisi Bülteni 2010; 1: 75-86.
10. Arikan S, Yücel AF, Kocakuşak A, Dadük Y, Adaş G, Onal MA. Retrospective analysis of the patients with penetrating cardiac trauma. Ulus Travma Acil Cerrahi Derg 2003; 9: 124- 8.
11. Felician DV, Moore EE, Biffl WL. Western trauma association critical decisions in trauma: management of abdominal vascular trauma. J Trauma Acute Care Surg 2015; 79: 1079-88.
12. Altun G, Azmak D, Yılmaz A. Yaşayan olgularda kesici-delici alet yaralanmaları. Adli Tıp Bülteni 2000; 5: 52-5.
13. Altundag MT, Ulucay T, Zeyfeloglu Y, et al. Izmir'de yapılmış mediko-legal otopsilerde büyük damar yaralanmaları saptanan olguların değerlendirilmesi. J For Med 2014; 28: 256-66.
14. Korkmaz T, Kahramansoy N, Erkol Z, Sarıçil F, Kılıç A. Acil servise başvuran adli olguların ve düzenlenen adli raporların değerlendirilmesi. Med Bull Haseki2012; 50: 14-20.
15. Çetin Erdoğan Z, Teyin A, Birben B, Çetin B, Şahiner GG, Hamamcı M. Acil serviste düzenlenen adli raporların değerlendirilmesi. Bozok Med J 2018; 8: 34-40.
16. Altun G, Azmak AD, Yılmaz A, Yılmaz G. Trakya Üniversitesi Tıp Fakültesi Acil Servisi'ne başvuran adli olguların özellikleri. Adli Tıp Bülteni 1997; 2: 62-6.

17. Kaçmaz IE, Uzakgider M, Basa CD, et al. Retrospective analysis of adult forensic cases admitted to the emergency medicine clinic and consulted with orthopedics and traumatology. J DEU Med 2020; 34: 43-52.
18. Ulucay T, Altundag MT, Yavuz MS, et al. Künt veya penetran kardiyak yaralanma sonucu ölümlerin retrospektif değerlendirilmesi, J For Med 2015; 29: 1-11.
19. Manduz Ş, Katrancıoğlu N, Bingöl H, Atlı H, Doğan K. Delici kardiyak yaralanmalar. Turkish J Thorac Cardiovasc Surg 2008; 16: 228-31.
20. Prichayudh S, Verananvattna A, Sriussadaporn S, et al. Management of upper extremity vascular injury: outcome related to the Mangled Extremity Severity Score. World J Surg 2009; 33: 857-63.

Original Article

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Evaluation of the efficiency of treatment in girls with central precocious puberty/rapidly progressive puberty via ultrasonography

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ABSTRACT

Introduction: Central precocious puberty (CPP) is defined as the development of secondary sexual characteristics in girls before the age of 8 years due to the activation of the hypothalamus-pituitary-gonadal (HPG) axis, and long-acting GnRH analogues (GnRHa) are used in its standard treatment. The gold standard method for evaluating the efficiency of treatment is to demonstrate the suppression of the LH response with the GnRH stimulation test. Pelvic ultrasonography (US) is an easily accessible, safe, free of ionizing radiation and non-invasive imaging method, which is used for the evaluation of internal genital organs, monitoring of sexual development, and excluding ovarian mass. This study aimed to evaluate the effect of GnRHa treatment on internal genital organs and to determine the role of pelvic ultrasonography in treatment follow-up.

Material and Method: Between January 2017 and May 2021, 50 girls who were started on GnRHa treatment due to the diagnosis of CPP or rapidly progressing puberty were followed up, and who underwent pelvic US imaging at the beginning of treatment and in the 1st year of treatment were included in the study. The clinical and sonographic findings were compared before and after the treatment.

Results: Of the 50 patients in the study, 52% (n=26) were being followed up with CPP, and 48% (n=24) with rapidly progressive puberty. In the first year of GnRHa treatment, while the suppression of the HPG axis was detected in 82% (n=41) of the cases with the GnRHa test, there was no suppression in 18% (n=9). A decrease in ovarian volume was observed in 73.2% (n=30) of 41 patients with suppression of the HPG axis, a decrease in uterine volume in 65.9% (n=27), and a decrease in uterine anterior-posterior size in 61% (n=25). While endometrial thickness could be measured in 64% (n=32) of the cases before treatment, measurable endometrial thickness was detected in only 6% (n=3) of the cases in the 1st year of treatment.

Conclusion: We detected in this study that GnRHa treatment in girls with a diagnosis of CPP/rapid puberty caused a significant regression in ovarian and uterus dimensions and endometrial echo selectability. Our results, in line with the literature, support that pelvic ultrasonography is an appropriate modality for monitoring the suppression of the HPG axis during CPP treatment and may reduce the need for repeated GnRH stimulation tests.

Keywords: Central precocious puberty, ultrasonography, GnRHa therapy, uterine diamater, ovarian volume

This study was presented as an oral presentation at the 42nd National Radiology Congress 2021 (SS-027)

INTRODUCTION

Central precocious puberty (CPP) is defined as the development of secondary sexual characteristics due to the activation of the hypothalamus-pituitary-gonad (HPG) axis before the age of 8 years in girls and 9 years in boys (1). The maturation of reproductive functions is dependent on the stimulation of increased pulsatile Gonadotropin-releasing hormone (GnRH) release into the pituitary portal circulation and, accordingly, pulsatile luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release into the peripheral circulation (2). FSH released from anterior pituitary gonadotroph cells with GnRH stimulation causes the growth of ovarian follicles and production of estrogen from androgens in girls (3). Estrogen levels fluctuate, but are usually measured in excess of 12 pg/ml.

Pelvic ultrasonography (US) is an easily accessible, safe, free of ionizing radiation and non-invasive imaging method for the evaluation of internal genital organs and

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gonads, monitoring sexual development, and excluding ovarian mass in girls (4,5). In prepubertal girls, uterine length should be less than 35 mm; over long diameter should not exceed 20 mm. Bilaterally large ovaries is one of the important criteria of CPP. An increase in uterine length (≥ 35 mm) and tubular shape of the uterus changing to pear-like appearance are determinative findings. The ovaries showing homogeneous or microcystic features before puberty acquire a multicystic or macrocystic/follicular structure. Endometrial echo may thicken and become selectability. Menarche usually begins when the endometrium thickness reaches 5 mm (6). Diagnosis is made by history, clinical findings, hormonal and radiological evaluation.

The aim of treatment in CPP is to suppress pulsatile gonadotropin release, to keep accelerated sexual maturation under control until normal pubertal age, to regress or stop sexual characteristics, to prevent premature closure of epiphyses, and to achieve adult target height. Long-acting GnRH analogues (GnRHa) have been used in the standard treatment of CPP since the 1980s. Puberty stages and growth of patients with CPP treated with GnRHa are evaluated every 3-6 months, and bone age is monitored periodically (7,8). Discontinuance or regression in the development of secondary sex characteristics, decreased growth rate to the prepubertal level, slowing of rapid progression in bone age (the ratio of bone age progression to chronological age progression<1.2) are clinical indicators of response to treatment (9). However, today, the gold standard in evaluating the efficiency of treatment is the GnRH stimulation test, and it is determined by showing the suppression of the LH response (10). However, the GnRH test is a laborious and invasive procedure that requires multiple blood sampling (11,12). This has led to the investigation of different methods to evaluate the HPG axis and response to treatment.

There are limited studies in the literature in which pelvic US is used to monitor GnRHa therapy in girls with CPP (12-16). Moreover, controversial results have been obtained about which pelvic US parameters are best in the evaluation of HPG axis suppression (12,14,16). This study aimed to evaluate the effect of GnRHa treatment on internal genital organs and to determine the role of pelvic ultrasonography in treatment follow-up.

MATERIAL AND METHOD

This study was approved by the Hitit University Faculty of Medicine, Non-interventional Researches Ethics Committee (Date: 26.05.2021, Decision No:2021-467). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 65 female patients who admitted to the Pediatric Endocrinology Polyclinic of our hospital with the complaint of early puberty and were diagnosed with CPP or rapidly progressive puberty (RPP) according to the following criteria and were treated with GnRHa.

- Secondary sex characters developed before the age of 8 years (CPP).
- RPP was diagnosed according to the appearance of breast buds between the ages of 8 and 10 years, accompanied by the presence of pubic or axillary hair and/or accelerated growth rate or bone age greater than 2 SD above chronological age (17).
- Increased levels of gonadotropins accepted in the pubertal interval (basal LH level of ≥0.3 mIU/mL or a peak LH response of ≥5 mIU/mL in standard intravenous GnRH tests).
- The following sonographic characteristics were considered as evidence of puberty: Ovarian volume > 2 mL, uterine length > 35 mm and pubertal configuration of uterus with a thickened endometrial echo > 2 mm (6).

GnRHa treatment was started when baseline LH or peak LH met the criteria given for CPP patients. In patients aged between 8 and 10 years (RPP group), GnRHa treatment was started in the presence of pubertal laboratory findings with rapid progression of pubertal findings. A rapid progression of pubertal findings was considered to be a one-stage progression of breast stage within 3–6 months and emergence of uterine length over 35 mm in pelvic US (18).

Initially, 65 female patients who were diagnosed with CPP or RPP in the Pediatric Endocrinology outpatient clinic between January 2017 and May 2021 and were started on GnRHa treatment (leuprolide acetate or triptorelin acetate, intramuscular or subcutaneous injection 3.75mg every 28 days) were included in the study. Fifteen of these patients were excluded from the study because they were receiving GnRHa therapy for less than 12 months or who had missing anthropometric measurements, physical examination or laboratory/radiological findings before or during treatment, or had irregular treatment and follow-up. Thus, 50 patients who had received GnRHa treatment for at least 12 months, who came for regular follow-ups, and who had anthropometric measurements, physical examination, and laboratory findings, as well as pelvic US and left wrist X-ray data before treatment and at the first year of treatment were included in the study. Patients with peripheral precocious puberty, organic CPP, chronic disease, and patients who were treated in another center before applying to our outpatient clinic were excluded.

The patients' chronological age (years), bone age (years), puberty stage, peak luteinizing hormone level in basal and GnRHa test, estradiol (E2) level , uterus transverse

and anterior-posterior (AP) diameter, uterus length, endometrial thickness, and bilateral ovarian 3 dimension determined by pelvic US were recorded retrospectively in the hospital information system. Uterine and ovarian volumes were calculated. The clinical and sonographic findings were compared before and after the treatment.

Clinical Follow-up

Children with basal LH levels above 0.3 mIU/mL, who also met the above criteria were accepted to have CPP/RPP if no GnRH stimulation test was performed. The GnRH stimulation test was performed after the intravenous administration of 0.1 mg of Gonadorelin acetate (gonadorelin acetate, Ferring®). LH and FSH levels were measured at 15, 30, 45, 60 and 90 minutes after injection (13,14,16). For patients diagnosed with CPP/RPP, treatment was started with GnRH analogue (3.75 mg as intramuscular or subcutaneous injection every 28 days). Physical examinations were made prior to and during the course of treatment at each follow-up visit once every 3 months, and staging of puberty was determined according to the criteria by Marshall and Tanner (19). The bone age was estimated by same pediatric endocrinologists (HNPK) using the Greulich and Pyle Atlas (20).

In order to evaluate the efficiency of the treatment, suppression of HPG axis was monitored with GnRHa tests at intervals of 3 months. Blood samples were collected for the measurements of basal LH, FSH, and E2 levels prior to intramuscular GnRHa injections and serum LH levels at 30 and 60 minutes following the injections. A peak LH response of <3 mIU/mL was accepted as the diagnostic criteria for suppressed HPG axis (21). Patients with peak LH levels of ≥3 mIU/mL were suspected to have nonsuppressed HPG axis, and, thus, the HPG axis of these patients was reassessed with standard intravenous GnRH tests 3 weeks after the GnRHa injection. The criterion for a suppressed HPG axis was a peak LH level of <2 mIU/mL in this test (22,23), and GnRHa doses for patients with a peak LH level of ≥2 mIU/mL were increased up to 7.5 mg every 28 days.

Hormone Analysis

Basal FSH, LH, and E2 levels were analyzed in blood samples collected between 8:00 and 8:30 a.m. The immunochemiluminometric assay (ICMA) method using commercial kits (ADVIA Centaur analyzer system, Bayer Diagnostics, USA) was used to measure FSH and LH levels.

Sonographic Evaluation

Transabdominal pelvic ultrasonography examination was performed by a single radiologist (NF) with 10 years of experience in the field, blind to clinical findings, when the cases had sufficient bladder fullness following 1 liter oral fluid intake 1-2 hours ago. Affiniti 70 ultrasound system (Philips Healthcare; Bothell, WA, USA), 3.5-5 Mhz frequency convex, and 9-12 Mhz frequency superficial probe were used. The width and AP dimension of the uterus was measured in the transverse plane, and the length of the uterus including the cervix in the longitudinal plane was measured in millimeters (**Figure 1**). Endometrial thickness and 3 dimensions of both ovaries were measured and recorded in both planes (**Figures 1-3**). The volume of the uterus and both ovaries was calculated using the ellipsoid formula (width × anterior-posterior dimension × length × 0.523).

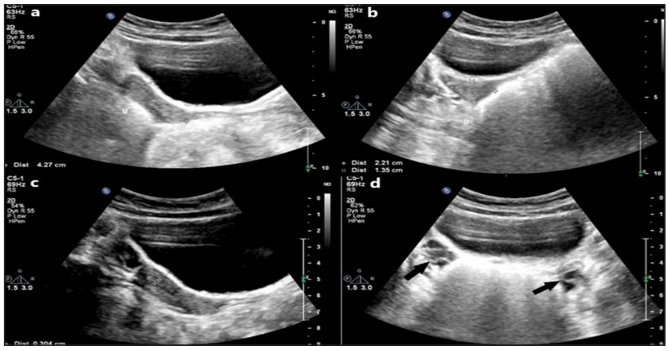

Figure 1. Transabdominal pelvic US imaging of internal genital organs in a 9-year-old girl a) Measurement of the length of the uterus including the cervix b) Measurement of the transverse and anterior-posterior size of the uterus c) Endometrial thickness measurement d) Imaging of the ovaries in the right and left posterolateral adjacent of the bladder (arrows).

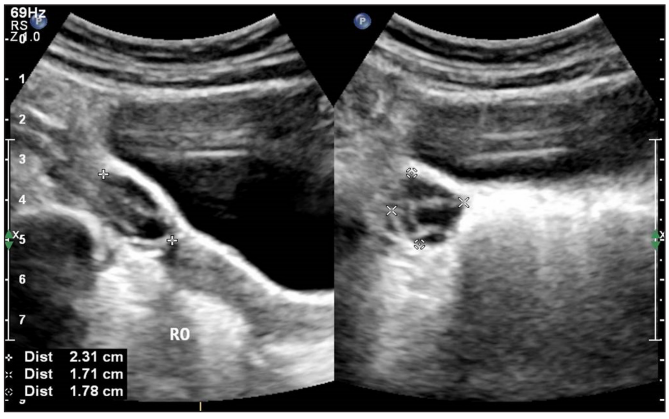

Figure 2. Sonographic measurement of right ovary 3 dimension of the same case

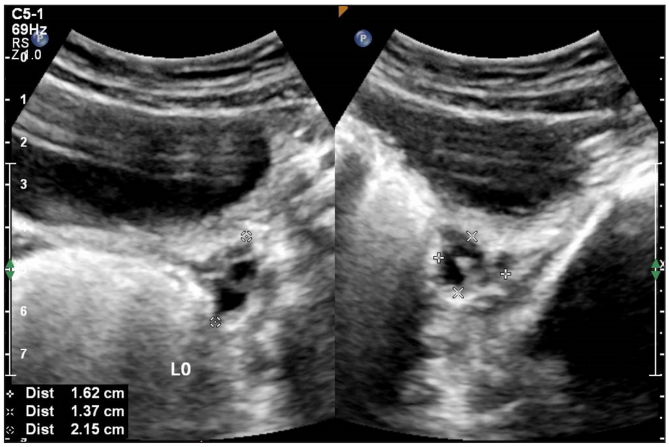

Figure 3. Sonographic measurement of left ovary 3 dimension of the same case

Statistical Analysis

Statistical analyses in our study were performed using the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normality distribution of the retrospective data was evaluated with the Kolmogorov–Smirnov test. Descriptive statistics for continuous variables were presented as mean ± standard deviation (SD) in normally distributed data, median (min-max) in non-normally distributed data, and categorical data as numbers and percentages (%). Student's t-test, Mann-Whitney U test were used to compare groups, and Fisher's chi-square test was used to compare group ratios. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 50 patients included in the study, 52% (n=26) were being followed up with the diagnosis of CPP, and 48% (n=24) with RPP. The clinical and laboratory findings of the cases are presented in **Table 1**.

It was determined that the uterine and ovarian volumes, uterine transverse, and AP size decreased statistically in the 1st year of the treatment compared to the beginning of the treatment (p<0.05) (**Table 2**). While endometrial thickness could be measured in 64% (n=32) of the cases before treatment, measurable endometrial thickness was detected in only 6% (n=3) of the cases in the 1st year of treatment. In the 1st year of GnRHa treatment, while the suppression of the HPG axis was detected in 82% (n=41) of the cases with the GnRHa test (the treatment was effective), there was no suppression in 18% (n=9). A decrease in ovarian volume in 73.2% (n=30) of 41 patients with suppression of the HPG axis, a decrease in uterine volume in 65.9% (n=27) of patients, a decrease in uterine AP size in 61% (n=25) of patients, a decrease in uterine transverse size in 56% (n=23) of patients and a decrease in uterine length in 48.7% (n=20) of the patients were observed. It was found that the most significant change in the internal genital organs was the decrease in the ovarian volume in the patients in whom the treatment was effective. The change in uterine dimensions was found to be more prominent in the AP dimension. There was no difference between the cases with and without suppression of the HPG axis in terms of age, pre-and post-treatment pubertal stage, bone age, estradiol level, and sonographic parameters (p>0.05).

Table 1. Clinical and laboratory findings of the cases before treatment and in the 1st year of treatment

	Pre-treatment (mean±SD) (min-max)	1st year of treatment (mean±SD) (min-max)	p
Chronological age (years)	7.99±1.36 (3.90-10.16)	8.99±1.36 (4.90-11.16)	<0.001
Bone age (years)	9.24±1.62 (3.50-13.50)	10.09±1.70 (4.00-14.00)	<0.001
Puberty stage	3* (2-5)	2* (1-5)	<0.001
Estradiol (pg/ml)	28.93±23.59 (5.00-89.00)	8.02±5.32 (5.00-25.10)	<0.001

*is the median value

Table 2. Pelvic US findings of the cases before treatment and in the 1st year of treatment

	Pre-treatment (mean ± SD) (min-max)	Post-treatment (mean ± SD) (min-max)	p
Uterus length (mm)	38.60±9.90 (17.00-55.00)	36.31±7.71 (14.0-50.0)	0.078
Uterine transverse size (mm)	18.25±6.71 (8.00-35.0)	15.43±4.83 (9.00-28.00)	0.001
Uterine AP size* (mm)	12.48±4.53 (7.00-25.00)	10.04±3.40 (5.00-22.00)	<0.001
Uterine volume (mm^3)	5245.32± 4328.38 (689.00-20625.00)	3126.90±2282.54 (504.00-10560.00)	<0.001
Right ovarian volume (mm^3)	2643.16±1582.47 (378.00-7744.00)	1827.48±1046.52 (31500-5049.00)	<0.001
Left ovarian volume (mm^3)	2582.40±1592.49 (308.00-6732.00)	1801.58±944.66 (315.00-4896.00)	<0.001
Total ovarian volume ** (mm^3)	2612.78±1534.55 (343.00-6167.00)	1814.53±966.98 (409.50-4972.50)	<0.001

*Uterine AP size: anterior posterior length measured from the uterine fundus section, **Total ovarian volume: Calculated as right ovarian volume+left ovarian volume/2.

DISCUSSION

In this study, we found regression in pubertal stages, decrease in E2 levels, uterus and ovarian volumes, more prominent in ovarian size and endometrial selectivity in the 1st year of GnRHa treatment in our CPP and RPP cases. It was noteworthy that the change in uterine dimensions was more pronounced in the AP dimension. GnRHa are known to be effective in the treatment of CPP. Post-treatment follow-up is important in order to provide parameters such as adherence to treatment, adequate dose, and to monitor adequate suppression. In the last few decades, a number of studies have been conducted to address the sonographic changes that occur in girls receiving GnRHa therapy (12,15,16,24). In the study of Jensen et al. (15) in which they examined 33 girls with idiopathic CPP treated with GnRHa, it was reported that the uterus and ovaries were larger than normal in 50% of the cases at the time of diagnosis and significantly regressed to age-appropriate normal values at the 3rd month after treatment. Yu et al. (16) evaluated 119 girls diagnosed with CPP and reported that pelvic US is a suitable and objective modality for monitoring the suppression of the HPG axis during CPP treatment and can reduce the need for repeat GnRH stimulation tests.

deVries et al. (12) concluded that pelvic US is an appropriate and objective method to monitor the suppression of the HPG axis during CPP treatment. In their study, they stated that the case in which GnRHa treatment was not effective and therefore the absence of sonographic

findings of these cases was the weakness of their study. In our study, although 18% of our patients did not have HPG axis suppression, we did not find any difference in terms of age, pre-and post-treatment puberty stage, bone age, E2 level, and sonographic parameters between the cases with and without suppression of the HPG axis. In addition, although the HPG axis was found to be suppressed by the GnRHa test, no decrease was found in the ovary volume in 11 patients and in the uterus volume in 14 patients. Ersen et al. (25) defined uterus and ovarian volumes in healthy Turkish girls according to age, and reported ovarian volume>1.58 cm3 (73% sensitivity and 48% specificity), uterine volume>2.57 cm3 (80% sensitivity and 50% specificity) as the threshold value for the onset of puberty. When the data of our patients were evaluated according to these threshold values, we had 9 cases with uterine and ovarian volumes in the normal range for age before treatment, and 14 cases with uterus or ovarian volumes within the normal range. After the treatment, the calculated volumes were within the normal range for age in 5 of 9 cases with both ovarian and uterine volumes in the normal range, in 11 of 14 cases with uterine volumes in the normal range, and in 10 of 14 cases with ovarian volumes in the normal range. We think that our results in the patient group who did not have a significant/apparent regression in uterus and ovary dimensions with treatment may be due to this occasion.

The time course of hormone-gonadal interaction in the diagnosis and treatment of CPP and the morphological changes that will occur in this process are important factors to consider when evaluating these patients. Ambrosino et al. (14) reported that a 3-month interval is required for the morphological changes to occur after GnRH treatment, the most significant improvement occurs after the 6th month, and the decrease in ovarian volume is the fastest morphological response. They noted that changes in the uterine size and configuration occur more slowly, with a later response, and reflect the general long-term trend. It was emphasized in another study that the ovarian changes were faster, the decrease in the uterine volume started after the 3rd month and continued at the 12th month (15).

On the other hand, there is some debate about which pelvic US is the best parameter to evaluate suppression of the HPG axis. Yu et al. found in their study that all parameters related to uterus/ovarian size and volumes were significantly decreased compared to pre-treatment measurements, and they reported uterine body volume as the best sonographic parameter to distinguish patients with CPP from normal girls (sensitivity 91%, specificity 68%)(16). In the same study, the other parameters with the highest sensitivity were found to be the uterus AP size and the ovarian volume (89%). Wen et al. (26) reported that the best parameter to distinguish the cases with CPP from normal girls in the 8-10 age group is the endometrial thickness, and they said that the cut-off value of 2.6 mm has a sensitivity of 76% and a specificity of 100%. deVries et al. (12) reported that the most important response to treatment is the uterine parameters and absence of endometrial echo, and they are better indicators than ovarian parameters. They suggested that each patient started the treatment with a different size of uterus, ovary, and different Tanner stage, and that there were individual differences, and to compare the pre-treatment and post-treatment sonographic parameters of the same patient., not the healthy control group. In our study, the most significant decreasing parameters in the follow-up of treatment efficiency were ovarian volume, uterine volume, and endometrial selectivity. Among the uterine size parameters, the AP size is the parameter with the most significant decrease, and we did not detect a significant decrease in the measured uterine length, including the cervix. In line with these data, we believe that it is necessary to combine multiple ultrasound parameters with clinical symptoms and sexual hormone levels in the diagnosis and treatment follow-up of CPP.

The limitations of our study are its retrospective design, small sample size, and lack of a control group consisting of healthy volunteers. Prospective studies involving longer-term ultrasonography results in girls diagnosed with CPP/RPP and treated with GnRHa are needed.

CONCLUSION

We found in this study that GnRHa treatment in girls with CPP or RPP caused a significant regression in ovarian and uterus dimensions and endometrial echo selectivity. Our results, in line with the literature, support the view that pelvic ultrasonography is a suitable modality for monitoring the suppression of the HPG axis in the evaluation of the efficiency of GnRHa therapy and may reduce the need for repeated GnRH stimulation tests.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Hitit University Faculty of Medicine, Non-interventional Researches Ethics Committee (Date: 26.05.2021, Decision No:2021-467).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Park J, Kim JH. Change in body mass index and insulin resistance after 1-year treatment with gonadotropin-releasing hormone agonists in girls with central precocious puberty. Ann Pediatr Endocrinol Metab 2017; 22: 27-35.
2. Partsch CJ, Heger S, Sippell WG. Management and outcome of central precocious puberty. Clin Endocrinol 2002; 56: 129-48.
3. Aycan, Z. Delayed puberty. Turkish Archives of Pediatrics 2011; 46: 88-91.
4. Stranzinger E, Strouse PJ. Ultrasound of the pediatric female pelvis. Semin Ultrasound CT MR 2008; 29: 98-113.
5. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev 2003; 24: 668-93.
6. Berberoğlu M. Puberty precocious. Turkish J Pediatr Dis 2010; 4: 61-4
7. Brito VN, Latronico AC, Arnhold IJ, Mendonça BB. Update on the etiology, diagnosis and therapeutic management of sexual precocity. Arq Bras Endocrinol Metabol 2008; 52: 18-31.
8. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009; 123: e752-62.
9. Bereket A. A critical appraisal of the effect of gonadotropin-releasing hormon analog treatment on adult height of girls with central precocious puberty. J Clin Res Pediatr Endocrinol 2017; 9: 33-48.
10. Brito VN, Latronico AC, Arnhold IJ, Mendonca BB. A single luteinizing hormone determination 2 hours after depot leuprolide is useful for therapy monitoring of gonadotropin-dependent precocious puberty in girls. J Clin Endocrinol Metab 2004; 89: 4338-42.
11. Calcaterra V, Sampaolo P, Klersy C, et al. Utility of breast ultrasonography in the diagnostic work-up of precocious puberty and proposal of a prognostic index for identifying girls with rapidly progressive central precocious puberty. Ultrasound Obstet Gynecol 2009; 33: 85-91.
12. de Vries L, Phillip M. Role of pelvic ultrasound in girls with precocious puberty. Horm Res Paediatr 2011; 75: 148-52.
13. Hall DA, Crowley WF, Wierman ME, Simeone JF, McCarthy KA. Sonographic monitoring of LHRH analogue therapy in idiopathic precocious puberty in young girls. J Clin Ultrasound 1986; 14: 331-8.
14. Ambrosino MM, Hernanz-Schulman M, Genieser NB, Sklar CA, Fefferman NR, David R. Monitoring of girls undergoing medical therapy for isosexual precocious puberty. J Ultrasound Med 1994; 13: 501-8.
15. Jensen AM, Brocks V, Holm K, Laursen EM, Müller J. Central precocious puberty in girls: internal genitalia before, during, and after treatment with long-acting gonadotropin-releasing hormone analogues. J Pediatr 1998; 132: 105-8.
16. Yu HK, Liu X, Chen JK, Wang S, Quan XY. Pelvic ultrasound in diagnosing and evaluating the efficacy of gonadotropin-releasing hormone agonist therapy in girls with idiopathic central precocious puberty. Front Pharmacol 2019; 10: 104.
17. Lemaire P, Pierre D, Bertrand JB, Brauner R. A mathematical model for predicting the adult height of girls with advanced puberty after spontaneous growth. BMC Pediatr 2014; 14: 172.
18. Onat PŞ, Erdeve ŞS, Çetinkaya S, Aycan Z. Effect of gonadotropin-releasing hormone analog treatment on final height in girls aged 6-10 years with central precocious and early puberty. Turk Pediatri Ars 2020; 55: 361-9
19. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child 1969: 44; 291-303.
20. Greulich WW, Pyle SI (editors). Radiographic atlas of the skeletal development of the hand and wrist. 2nd ed., Stanford, CA: Stanford University Press, 1959.
21. Bhatia S, Neely EK, Wilson DM. Serum luteinizing hormone rises within minutes after depot leuprolide injection: implications for monitoring therapy. Pediatrics 2002; 109: E30. X
22. Lawson ML, Cohen N. A single sample subcutaneous luteinizing hormone (LH)-releasing hormone (LHRH) stimulation test for monitoring LH suppression in children with central precocious puberty receiving LHRH agonists. J Clin Endocrinol Metab 1999; 84: 4536-40.
23. Kendirci HN, Ağladıoğlu SY, Baş VN, Önder A, Çetinkaya S, Aycan Z. Evaluating the efficacy of treatment with a GnRH analogue in patients with central precocious puberty. Int J Endocrinol 2015; 2015: 247386.
24. Ben-Haroush A, Goldberg-Stern H, Phillip M, de Vries L. GnRH agonist treatment in girls with precocious puberty does not compromise post-pubertal uterine size. Hum Reprod 2007; 22: 895-900.
25. Ersen A, Onal H, Yıldırım D, Adal E. Ovarian and uterine ultrasonography and relation to puberty in healthy girls between 6 and 16 years in the Turkish population: a cross-sectional study. J Pediatr Endocrinol Metab 2012; 25: 447-51.
26. Wen X, Wen D, Zhang H, Zhang H, Yang Y. Observational study pelvic ultrasound a useful tool in the diagnosis and differentiation of precocious puberty in Chinese girls. Medicine (Baltimore) 2018; 97: e0092.

Original Article

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Significant and nonsignificant findings on magnetic resonance imaging of patients with headache

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ABSTRACT

Aim: The great majority of people suffer from headaches. Neuroimaging has a very limited role in determining the etiology of headache However, neuroimaging, especially magnetic resonance imaging (MRI), is requested for the vast majority of patients with headache. We aimed to determine the frequency of clinically significant and nonsignificant findings on brain MRI in patients with headache, and the factors associated with these findings.

Material and Method: A total of 350 patients (231 women and 119 men), who underwent MRI examinations for headache complaints, were included in the study. Based on the evaluation of lesions detected on MRI and headache characteristics together, lesions associated with headache were classified as significant findings, and lesions unrelated to headache were classified as nonsignificant findings. Patients were compared in terms of brain MRI findings on the basis of age, gender, and duration of headache complaints.

Results: Assessment of brain MRIs revealed normal findings in 211 (60.3%) patients, nonsignificant findings in 122 (34.8%) patients, and significant findings that could cause headache in 17 (4.9%) patients. The most common significant lesions were acute sinusitis, acute cerebrovascular accident, cerebral venous sinus thrombosis and aneurysm. In patients over 65 years of age, the frequency of significant findings was significantly higher (p:0.001). The frequency of significant findings was higher in male patients and patients with a headache duration of less than one month, but there was no statistical difference (p:0.452 and p:0477).

Conclusion: We found significant findings on brain MRI in approximately 5% of patients with headache. Being over 65 years old and acute onset headache increase the probability of detecting significant lesions on MRI. Despite its low diagnostic value, physicians will often refer patients with headaches to neuroimaging for fear of missing a critical underlying lesion and encountering medico-legal issues. Taking into account worrying red flags can increase the likelihood of finding significant lesions.

Keywords: Headache, neuroimaging, magnetic resonance imaging

INTRODUCTION

Headache is one of the most common complaints in population. Its lifetime prevalence is over 90% (1). All health care providers, especially neurologists, frequently encounter the problem of headache. According to the International Headache Society classification, headaches are divided into two basic groups: primary and secondary. There is no underlying detectable cause of primary headaches. The most common primary headache types are tension-type headache and migraine. In secondary headaches, headaches appear as a symptom depending on an underlying cause such as infection, metabolic disorder, vascular diseases, trauma, and brain tumors (2,3).

Today, as in the past, the history and physical examination findings play a significant role in the differential diagnosis of headache. However, with rapid technological advancements, numerous diagnostic methods, particularly brain magnetic resonance imaging (MRI), have become widely used in the differential diagnosis of headache. Brain MRI findings are usually normal in the vast majority of patients with headache (4,5). However, nowadays, physicians frequently utilize neuroimaging techniques to exclude life-threatening secondary causes of headaches. Other reasons for the frequent use of neuroimaging methods are patient requests and medico-legal concerns (5–8).

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The excessive usage of neuroimaging, particularly MRI, has increased the likelihood of incidental lesion detection (7,9,10). The detected incidental lesions can sometimes entangle the diagnosis process rather than contributing in the accurate diagnosis. Sometimes, headache is attributed to these incidental lesions, and detailed evaluation of the patients' mental, hemodynamic and metabolic conditions is ignored (9). Therefore, the diagnosis of the actual problems underlying the headache may be delayed.

Some studies have brought attention to certain important red flags that predict the possibility of detecting a significant lesion on MRI in patients with headache (3,11). Therefore, it has been proposed that applying neuroimaging in selected cases under the guidance of these red flags will contribute to a cost-effective process as well as help early diagnosis (3,5,7,12,13).

In this study, we aimed to determine the frequency of clinically significant and nonsignificant findings on brain MRI in patients with headache and investigate the relationship of these findings with the characteristics of headache and demographic data of the patients.

MATERIAL AND METHOD

This retrospective study was approved by Ankara City Hospital No: 1 Clinical Research Ethics Committee (Date: 2022, Decision No: E1/2295/2022). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who presented to our neurology outpatient clinic in September 2019 and October 2019 with complaints of headache were analyzed retrospectively. Patients with a history of primary headache and known intracranial neoplasia were not included in the study. Patients who had recently had a head injury were also excluded from the study. A total of 350 patients, 231 (66%) women and 119 (34%) men, who underwent MRI examinations for headache complaints, were included in the study.

The patients' age, gender, smoking habits, comorbid diseases, and headache duration were all recorded. If patients have other complaints accompanying headache and abnormal neurological examination findings, this information was recorded.

Two expert neurologists reviewed the brain MRI scans and reports. The detected lesions and the headache characteristics of the patients were compared:

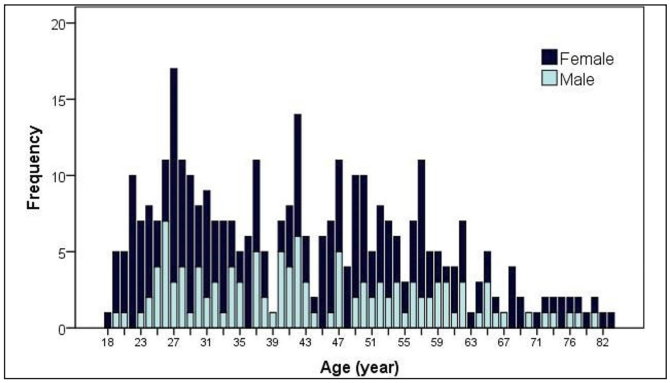
- Lesions corresponding to the headache characteristics were accepted as “significant lesions”.
- Lesions that did not correspond with the headache characteristics were accepted as "nonsignificant (incidental) lesions".

The patients were divided into three different groups according to the duration of the headache (less than one month and one month or more), age (under 65 years old and over 65 years old), and gender. Based on these groupings, patients were compared in terms of brain MRI findings.

All statistical analyses were done using IBM SPSS statistic 22.0 (Chicago, IL, USA). Numerical variables were expressed as mean±SD. Comparisons of numerical variables were made using Student's t-test. Categorical variables were compared using the Chi-Square test. A $p<0.05$ level was considered statistically significant.

RESULTS

The mean age was 42.63±15.06 years (**Graphic 1**). The study group consisted of 231 (66%) female and 119 (34%) male patients. The mean duration of headache complaint was 23.37±27.27 months. The two most common comorbid diseases detected in our patients were hypertension (80 patients, 22.9%) and psychiatric disorders (68 patients, 19.4%). Other common comorbid diseases are shown in **Table 1**.



Graphic 1. Age and gender distribution of patients with headache

Assessment of brain MRIs revealed normal findings in 211 (60.3%) patients, insignificant findings in 122 (34.8%) patients, and significant findings that could cause headache in 17 (4.9%) patients. The most common significant finding in the patients was sinusitis (5 patients, 1.4%). One of the patients with acute cerebrovascular accident (CVA) presented with only headache, and the neurological examination was normal. However, MRI showed multiple sub-acute millimetric infarcts. In the other acute CVA patient who presented with headache and tinnitus, no significant abnormal finding was detected in the neurological examination. MRI demonstrated acute 4 millimeters (mm) left cerebellar infarction. One of the two patients with acute cerebral venous sinus thrombosis presented with headache only, while the other had eyelid twitching and headache complaints. There were no significant

abnormal findings in the neurological and funduscopic examinations of both. The patient with pseudotumor cerebri had a complaint of headache and decreased vision in the left eye. Fundoscopic examination revealed papilledema on the left side. MRI of the patient with pseudotumor cerebri demonstrated that the height of the pituitary gland decreased according to the patient's age, slight enlargement of the suprasellar cisterna, and prominent subarachnoid space around the optic nerves.

The three most common nonsignificant findings in our study group were white matter hyperintensity (52 patients, 14.9%), paranasal sinus problems (26 patients, 7.4%), and arachnoid cysts (13 patients, 3.7%). In three patients with meningioma, the lesions were smaller than 5 mm and did not have a critical localization. Parietal capillary telangiectasia was found in one of the two patients with vascular malformation, and a frontal hemangioma smaller than 5 mm was found in the other. In two patients with Chiari malformation, downward displacement was shorter than 3 mm. We detected choroid plexus lesions in three of our patients. One of our patients had mild contrast enhancement in the choroid plexus, the other had a small papilloma, and the last one had small xanthogranulomas in lateral ventricles. These lesions were insufficient to explain the headache complaints of our patients. We detected partial empty sella in two of our patients. None of them were associated with pseudotumor cerebri.

All of the rare significant and nonsignificant findings are presented in **Table 1**.

During the investigation of the etiology of headache, 13 (3.7%) patients were diagnosed with hypertension. In 11 of the newly diagnosed hypertension cases, the duration of the headache complaint was less than 12 months. No significant finding was detected in MRI in any of these cases.

Psychiatric comorbidity was detected in 68 patients, including anxiety in 43 patients, depression in 20 patients, obsessive-compulsive disorder in 3 patients, and psychotic disorder in 2 patients. Only one (1.5%) of these cases had a significant finding (pituitary macroadenoma) on brain MRI.

Thirty-one (%8.9) of our patients were aged 65 and over. When we grouped our patients as <65 years and ≥65 years of age, the difference between the groups in terms of brain MRI findings was statistically significant (p:0.001). While 63.6% of patients under 65 years of age had normal brain MRI findings, only 22.6% of patients 65-year-old or older had normal brain MRI findings. Both significant (12.9%) and nonsignificant (64.5%) brain MRI findings were found to be significantly more common in the 65-year-old or older group (**Table 2**).

Table 1. Demographic and clinical data of the study group

	All Cases (n:350)
Age (year)	42.63±15.06
Gender Female/Male	231 (66%)/119 (34%)
Smoking	44 (12.6%)
Duration of headache complaint (month)	23.37±27.27
Comorbidities	
Coronary artery disease	21 (6.0%)
Hypertension	80 (22.9%)
Hyperlipidemia	19 (5.4%)
Diabetes mellitus	29 (8.3%)
Neurological diseases	17 (4.9%)
Psychiatric diseases	68 (19.4%)
Anxiety	*43 (12.2%)*
Depression	*20 (5.7%)*
Obsessive-compulsive disorder	*3 (0.9%)*
Psychotic disorder	*2 (0.6%)*
Newly diagosed hypertension cases	13 (3.7%)
Brain magnetic resonance imaging findings	
Normal	***211 (60.3%)***
Nonsignificant findings	***122 (34.8%)***
White matter hyperintensity	52 (14.9%)
Paranasal sinus diseases	26 (7.4%)
Arachnoid cyst	13 (3.7%)
Atrophy	10 (2.9%)
Cerebral-cerebellar atrophy	*4 (1.2%)*
Cerebral atrophy	*5 (1.4%)*
Focal atrophy	*1 (0.3%)*
Encephalomalasic changes	5 (1.4%)
Meningioma	3 (0.9%)
Choroid plexus lesion	3 (0.9%)
Chiari malformation	2 (0.6%)
Empty sella	2 (0.6%)
Pineal cyst	2 (0.6%)
Vascular malformations	2 (0.6%)
Neuroglial Cyst	1 (0.3%)
Colpocephaly	1 (0.3%)
Significant findings	***17 (4.9%)***
Sinusitis	5 (1.4%)
Acute cerebrovascular accident	2 (0.6%)
Acute cerebral venous sinus thrombosis	2 (0.6%)
Aneurysm	2 (0.6%)
Otitis media	2 (0.6%)
Triventricular hydrocephalus	1 (0.3%)
Pituitary macroadenoma	1 (0.3%)
Cavernous hemangioma	1 (0.3%)
Pseudotumor cerebri	1 (0.3%)

Table 2. Comparison of patients' MRI findings grouped by age, duration of headache and gender

	Normal findings n: 210	Nonsignificant findings n: 123	Significant findings n: 17	p
Age (year)				0.001
< 65	203 (63.6%)	103 (32.3%)	13 (4.1%)	
≥ 65	7 (22.6%)	20 (64.5%)	4 (12.9%)	
Duration of headache complaint				0.477
< 1 month	49 (55.7%)	33 (37.5%)	6 (6.8%)	
≥ 1 month	161 (61.5%)	90 (34.4%)	11 (4.2%)	
Gender				0.452
Female	142 (61.5%)	80 (34.6%)	9 (3.9%)	
Male	68 (57.1%)	43 (36.1%)	8 (6.7%)	

When the patients were grouped as those with headache less than one month (88 patients, 25.1%) and those with one month or longer (262 patients, 74.9%), no significant difference was found between the groups in terms of brain MRI findings (p:0.477). Although it was not statistically significant, the frequency of significant findings was higher in patients with headache less than one month old (6.8%) (**Table 2**).

When the patients were compared by gender, significant brain MRI findings were observed more frequently in male patients (6.7%) than in female patients (3.9%), but there was no statistical difference (p:0.452) (**Table 2**).

DISCUSSION

We found significant lesions associated with headache on brain MRI of approximately 5% of patients. On MRI of approximately one-third of the patients, we detected incidental lesions unrelated to the described headache characteristics. The incidence of significant lesions on brain MRI was significantly higher in elderly patients. The most common comorbid diseases in patients presenting with headaches were hypertension and psychiatric diseases. The frequency of significant lesions associated with headache on brain MRI was rare in patients with psychiatric comorbidities. Newly diagnosed hypertension was common in patients with headache complaint duration of less than one year.

Headache is among the most common complaints in both men and women. The majority of headaches are primary headaches. Secondary headaches caused by underlying pathologies such as vessels, nerves, and other structures in the head and neck region, and systemic diseases are less common than primary headaches (1,3). While neurological examination findings and neuroimaging findings are generally normal in primary headaches, significant pathological lesions can be seen on neuroimaging in a small portion of secondary headaches. Therefore, people suffering from headaches should be carefully and extensively investigated (3,11).

In the evaluation of headaches, careful patient history and detailed neurological examination are the most critical steps. Theoretically, in the light of the information obtained from the history and neurological examination, it should be decided whether a further examination is needed (3,9,13). However, a significant portion of patients with headache complaints are directed to neuroimaging in daily hospital practices (9). In studies, neuroimaging has detected significant lesions in a very small proportion of patients with headaches. The frequency of finding significant lesions on neuroimaging has been reported between 0.18% and 2.1%.(7,14) However, in our study, we found significant findings that could explain the headache on brain MRI in only 4.9% of our patients. The frequency of detecting significant lesions in our study was slightly higher than in other studies. One of the reasons for this situation may be that we did not include patients with a previous primary headache diagnosis in our study because neurological imaging findings are mostly normal in these patients. Another reason may be that we accept the signs of acute sinusitis as a significant lesion.

Neuroimaging helps to diagnose very few patients during the evaluation of headaches. Thus the reasons for its overuse are still open to debate. Today, neuroimaging tests are preferred as an exclusion tool for serious underlying pathologies rather than a diagnostic test when investigating the etiology of headaches (1,5,7). The physician's fear of missing a significant lesion that may cause headaches is an important reason for the frequent use of neuroimaging. Another reason is the concerns of the patients and their relatives over the ongoing headache. Increasing medico-legal problems in recent years is another important reason. Under the pressure of patient worry on the one hand and medico-legal reasons on the other, the physician tends to use neuroimaging despite the absence of any medical indications (12,15–17).

In recent years, significant advances have been made in neuroimaging devices, including MRI. Advances in imaging techniques allow good characterization of detected lesions. However, advances in imaging technology have often led to detecting clinically nonsignificant incidental lesions and anatomical variants (10). Under the influence of the same medico-legal concerns, radiologists started to report these clinically nonsignificant incidental lesions in detail. As a result, insignificant incidental lesions, which may even be multiple, on brain MRI reports have increased rather than reduced both the clinician's and the patient's concerns. Furthermore, sometimes these incidental lesions and detailed defensive reports lead the physician to refer to invasive procedures such as lumbar puncture and angiography in the differential diagnosis of headaches (7,8,15). These invasive procedures cause an increased medical and economic burden as well as significant problems such as increased complication occurrence. The incidence of incidental lesions in patients with headaches has been reported between 4.3% and 46% (10,14). In our study, we found incidental lesions unrelated to their headache in 35.1% of patients on brain MRI. Consistent with the literature, most of the incidental lesions in our patients consisted of benign changes that occur with aging, such as white matter hyperintensities and atrophy and some structural changes.

Some authors have drawn attention to various red flags that suggest significant lesions that may cause headaches in patients. They emphasized the increase in the probability

of identifying significant findings on brain MRI in the presence of these red flags. It has been proposed that headaches, which start at advanced ages, may sometimes occur secondary to serious diseases (11,13,15). We found a high rate (12.9%) of significant findings on brain MRI in our patients aged 65 years and older with headaches. Acute headache has also been considered as a predictor of significant lesions. The chance of detecting significant findings on MRI in acute-onset headaches can reach 20%, especially in selected cases (12). We found the frequency of significant findings slightly higher in cases with headache onset less than one month compared to other patients. In a previous study, the female gender was found to be a risk factor for significant MRI findings (12). However, in some other studies, significant findings on neuroimaging were found more frequently in male patients (8,15). In our study, the frequency of significant findings on brain MRI was higher in male patients than in female patients, but the difference was insignificant. In addition, changes in headache character, gradual increase in pain intensity and presence of other symptoms accompanying headache are risk factors for detecting significant findings in MRI (12–14). Budweg et al. (12) showed that approximately half of the patients with significant findings on brain MRI had positive neurological examination findings.

Comorbid diseases such as hypertension, metabolic, cardiovascular, neurological, and psychiatric diseases are frequently observed in patients with headaches (18). Akyıldız et al. (19) reported the prevalence of psychiatric disease in patients with headaches at a very high rate of 80%. Psychiatric disorders were the second most common comorbid disease in our study population. We found less frequent significant findings on brain MRIs of patients with psychiatric comorbidities. The relationships between psychiatric diseases and headaches are complex and multifaceted. Psychiatric diseases have a negative effect on headache management (18,20). Therefore, the evaluation of headache patients with psychiatric comorbidity together with a psychiatrist may affect the rate of need for MRI in the differential diagnosis of these patients.

In our study, the most common comorbid disease accompanying headache was hypertension. In addition, we found a high frequency of newly diagnosed hypertension among patients with a headache complaint of less than a year. Providing effective blood pressure control in these patients may reduce headache complaints, and as a result, unnecessary MRI can be avoided. On the other hand, close monitoring of blood pressure before starting further investigations in middle-aged patients with headaches may enable us to detect new-onset hypertension cases that are overlooked and may reduce the need for further investigations.

CONCLUSION

We found significant findings on brain MRI of 5% of patients with headaches. Being over 65 years old and acute onset headache increase the probability of detecting significant lesions on MRI. When neuroimaging is requested in the differential diagnosis of patients presenting with headaches, informing patients about possible nonsignificant incidental lesions will reduce the concerns of patients and their relatives. Although its diagnostic ability is low, physicians will continue to use neuroimaging frequently in patients with headaches to avoid missing a critical underlying lesion and not be entangled with medico-legal problems. However, considering alarming red flags may increase the probability of finding significant lesions.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Ankara City Hospital No: 1 Clinical Research Ethics Committee (Date: 2022, Decision No: E1/2295/2022).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Robbins MS. Diagnosis and management of headache: a review. JAMA. 2021; 325: 1874-85.
2. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018; 38: 1-211.
3. Rizzoli P, Mullally WJ. Headache. Am J Med 2018; 131 :17-24.
4. Evans RW. Incidental findings and normal anatomical variants on MRI of the brain in adults for primary headaches. Headache 2017; 57 :780-91.
5. Kenteu B, Fogang YF, Nyaga UF, Zafack JG, Noubiap JJ, Kamtchum-Tatuene J. Neuroimaging of headaches in patients with normal neurological examination: protocol for a systematic review. BMJ Open 2018; 8: e020190.
6. Bafaraj SM. Evaluation of neurological disorder using computed tomography and magnetic resonance imaging. JBM 2021; 09: 42-51.
7. Micieli A, Kingston W. An approach to identifying headache patients that require neuroimaging. Front Public Health 2019; 7: 52.

8. Sempere A, Porta-Etessam J, Medrano V, et al. Neuroimaging in the evaluation of patients with non-acute headache. Cephalalgia 2005; 25: 30-5.
9. Flores-Montanez Y, Nahas SJ. Unusual brain MRI findings in patients imaged for headache: a case series. Curr Pain Headache Rep 2020; 24 :51.
10. Morris Z, Whiteley WN, Longstreth WT, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2009; 339: b3016-b3016.
11. Do TP, la Cour Karottki NF, Ashina M. Updates in the diagnostic approach of headache. Curr Pain Headache Rep 2021; 25: 80.
12. Budweg J, Sprenger T, De V-T, Hagenkord A, Stippich C, Berger C. Factors associated with significant MRI findings in medical walk-in patients with acute headache. Swiss Med Wkly 2016; 146: w14349.
13. Goadsby PJ. To scan or not to scan in headache. BMJ 2004; 329: 469-70.
14. Clarke CE, Edwards J, Nicholl DJ, Sivaguru A. Imaging results in a consecutive series of 530 new patients in the Birmingham Headache Service. J Neurol 2010; 257: 1274-8.
15. Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM. Does this patient with headache have a migraine or need neuroimaging? JAMA 2006; 296 :1274-83.
16. Johnston JC, Wester K, Sartwelle TP. Neurological Fallacies Leading to Malpractice. Neurol Clin 2016; 34: 747-73.
17. Nahed BV, Babu MA, Smith TR, Heary RF. Malpractice liability and defensive medicine: a national survey of neurosurgeons. PLoS One 2012; 7: e39237.
18. Caponnetto V, Deodato M, Robotti M, et al. Comorbidities of primary headache disorders: a literature review with meta-analysis. J Headache Pain 2021; 22: 71.
19. Akyildiz K, Sercan M, Yildiz N, Cevik A, Kiyan A. Is headache only headache? comorbidity of headaches and mental disorders. DAJPNS 2015; 2828: 34-46.
20. Smitherman TA, Baskin SM. Headache secondary to psychiatric disorders. Current Science Inc 2008; 12: 305-310.

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Comparison of geriatric pulmonary embolism severity index (G-PESI) with PESI and s-PESI in predicting prognosis and mortality

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ABSTRACT

Aim: Our objective is to investigate the effect of geriatric pulmonary embolism severity index score on mortality independent of age and to compare it with pulmonary embolism severity index and simplified pulmonary embolism severity index.

Material and Method: This is a retrospective observational study including patients over 65 years of age diagnosed with pulmonary embolism, who presented to the emergency medicine clinic of tertiary hospital between January 1, 2016 and January 1, 2021. The relationship between the original PESI and 30-day mortality was evaluated, and age was removed from the original score in the G-PESI. A univariate analysis of PESI, s-PESI, and G-PESI was performed using the chi-square test, Fisher's exact test, Student's t-test, and Mann–Whitney U test as appropriate to determine the association of these scores with 30-day mortality. Statistical analysis was performed using SPSS version 26.0.

Results: This study included 167 patients, of whom 113 (67.7%) were women. According to the diagnostic test performance analysis report, the pulmonary embolism severity index, simplified pulmonary embolism severity index and geriatric pulmonary embolism severity index scores were statistically significant in predicting mortality, with the area under the curve values of 0.736 (0.34-1.91), 0.635 (0.74-1.81), and 0.739 (0.50-2.18) at the cut-off values of >110, >2, and >40, respectively ($p<0.001$, $p<0.001$, and $p=0.004$ respectively). When the area under the curve values of these three scores were compared, there was no statistically significant difference between pulmonary embolism severity index and geriatric pulmonary embolism severity index ($p=0.7241$).

Discussion: Geriatric pulmonary embolism severity index, similar to pulmonary embolism severity index, can be accepted as an independent predictor in geriatric patients diagnosed with pulmonary embolism.

Keywords: Geriatrics, PESI, pulmonary embolism

INTRODUCTION

Pulmonary embolism is a clinical condition that increases its age and requires urgent diagnosis and treatment. Particularly in geriatric patients, diagnosing pulmonary embolism and initiating treatment are quite challenging because these patients often do not present with common pulmonary embolism symptoms, and their complaints are not characterized by a sudden onset (1, 2). Clinical manifestations such as tachycardia, tachypnea, and venous thromboembolism, which are common, especially in high-risk cases of pulmonary embolism, are less frequently observed in geriatric patients (3). Furthermore, while some patients are diagnosed with pulmonary embolism based on a single clinical finding, other cases with more than one clinical finding consistent with this condition may receive a different diagnosis (3). Moreover, computerized tomography angiography (CTA), which is required for a definitive diagnosis in geriatric patients with suspected pulmonary embolism, may be not performed due to both the associated cost and a suspected contraindication (4,5). Difficulties in the management of anticoagulant therapy after diagnosis and the risk of complications are also significant in geriatric patients (5).

Along with the difficulties in the diagnosis process and patient management, there may be difficulties in estimating the prognosis of the geriatric patient diagnosed with pulmonary embolism, and it is believed that age affects the prognosis a lot. Aujesky et al. introduced the pulmonary embolism severity index (PESI), which consists of 11 criteria, including age, saturation, blood pressure, and

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comorbidities. The PESI, in which the age criterion is an important factor considered the most comprehensive score for estimating 30-day mortality in pulmonary embolism (6). This scoring system, which includes patients of all ages diagnosed with pulmonary embolism, predicts a higher risk in geriatric patients. This situation may affects the increase the intensive care and service hospitalization rates of the patients and the length of hospital stay during the management. The PESI was later simplified (s-PESI) or modified in some studies to compare the effectiveness of different versions in predicting mortality (7,8). Age criterion has an important place in these scoring systems.

In determining risk scores, it is important that the criteria be not only easy to evaluate but also sufficiently comprehensive to predict the clinical prognosis of patients. G-PESI, which was created only with vital signs and comorbid diseases and was formed by completely removing age from 11 criteria of PESI, was planned to question whether we have the possibility to predict the prognosis of pulmonary embolism regardless of age. The aim of our study was to investigate the effectiveness of the geriatric PESI (G-PESI) in predicting mortality regardless of age and to compare it with the PESI and s-PESI.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Ümraniye Education and Research Hospital Clinical Researches Ethics Committee (Date: 17.06.2021, Decision No: B.10.1.TKH.4.34.H.GP.0.01/191). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This was a retrospective observational study evaluating patients who presented to the emergency clinic of Turkey University of Health Sciences, Ümraniye Education and Research Hospital between January 1, 2016 and January 1, 2021. Our hospital is a tertiary center with 836 beds and 2.8 million resentations a year, of which 600,000 are made to the emergency department.

Study Population

Patients over 65 years of age who presented to the emergency department and were diagnosed with pulmonary embolism by CTA were evaluated using the hospital's computer-based data system (health information system). According to their mortality status, the patients were divided into two groups: survivors and non-survivors. A mortality analysis was conducted using the National Death Notification System which shows deaths from all causes. Patients with missing data or unknown outcomes were excluded from the study.

Data Collection

The collected data included age, sex, comorbidities (coronary artery disease, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, chronic kidney disease, cerebrovascular disease, congestive cardiac failure, and malignancy), Glasgow Coma Scale (GCS) score, vital signs, PESI, G-PESI, and s-PESI scores and clinical outcomes (ward admission, intensive care unit [ICU] admission, referral to an external center, 30-day mortality and discharge from the emergency department.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0. The conformity of the variables to the normal distribution was examined using visual (histograms and probability graphs) and statistical (Kolmogorov–Smirnov test) methods. The normality of continuous data was assessed using the Shapiro–Wilk test. The chi-square test was used in the analysis of categorical data, and Fisher's exact test was used when required. Quantitative variables were presented as medians and interquartile ranges (25^{th}–75^{th} percentiles). The Mann–Whitney U test was used for comparisons between two groups. The Bonferroni correction was applied to multiple comparisons. A univariate analysis of PESI, s-PESI, and G-PESI was performed using the chi-square test, Fisher's exact test, Student's t-test, and Mann–Whitney U test as appropriate to determine the association of these scores with 30-day mortality. A regression analysis was also performed to identify independent predictors of mortality. We also performed a receiver operating characteristic curve (ROC) curve analysis to explore the ability of the three indexes to predict survival. A ROC analysis was performed to evaluate the performance of the three scores in predicting mortality, and the area under the curve (AUC) values were calculated to determine their sensitivity, specificity, accuracy, and 95% confidence intervals. AUC values greater than 0.8 are required to predict mortality accurately. Although AUC values of 0.7–0.8 differ from the random value, they can be accepted as good predictors (9,10). Values of $p<0.05$ were considered statistically significant.

Geriatric PESI

The relationship between the original PESI and 30-day mortality was evaluated, and age was removed from the original score in the G-PESI. Thus, the G-PESI included the following criteria: sex, history of cancer, history of heart failure, history of chronic lung disease, heart rate of ≥110 beats per minute and systolic blood pressure <100mmhg. Using a method like that of the original PESI, the s-PESI was also used to predict mortality within 30 days of follow-up. A ROC analysis was performed to determine the optimal cutoff score of the

s-PESI for identifying low-risk patients. The cutoff was obtained by selecting the point of the test values that yielded the greatest sum of sensitivity and specificity (i.e., the point closest to the upper left corner of the ROC curve).

RESULTS

The study included 167 patients, of whom 113 (67.7%) were female. The 30-day mortality rate was 26.95%, and 73.3% of the patients who died were female. The median age of all the patients was 77 (65–97) years, and that of the patients in the non-survivor group was 76 (65–95) years, indicating no statistically significant difference between the survivor and non-survivor groups (p=0.823). **Table 1** presents the relationships between mortality and the vital signs, comorbidities of the patients. Most (65.9%) patients were referred to ward services, whereas 30.5% were admitted to the ICU. In the non-survivor group, 84.4% of the patients died after ICU admission, and there was a statistically significant relationship between intensive care requirement and mortality (p<0.001). Conversely, no statistically significant relationship was found between the length of hospital stay and mortality (p=0.117).

The PESI, s-PESI, and G-PESI scores were significantly associated with mortality (p<0.001, p=0.006, and p<0.001, respectively). According to the s-PESI risk classification, 90.4% of all patients and 97.8% of the patients in the non-survivor group were classified as high-risk cases (**Table 1**).

Table 1. Demographic data, symptoms, laboratory findings, and the PESI, s-PESI and G-PESI scores

Variables	Total	Survivor	Non-survivor	p value
	167 (100%)	122 (73.05%)	45 (26.95%)	
Age, years				0.823
Median	77 (64-97)	78 (64-97)	76 (64-95)	
Mean	77±8	77±7	77±8	
Gender				0.342
Male	54 (32.3%)	42 (34.4%)	12 (26.7%)	
Female	113 (67.7%)	80 (65.6%)	33 (73.3%)	
Comorbidities				
Hypertension	70 (41.9%)	51 (41.8%)	19 (42.2%)	0.961
Diabetes mellitus	30 (18%)	22 (18%)	8 (17.8%)	0.97
Chronic obstructive pulmonary disease	24 (14.5%)	20 (16.5%)	4 (8.9%)	0.213
Coronary artery disease	28 (16.8%)	22 (18%)	6 (13.3%)	0.471
Congestive heart failure	16 (9.6%)	8 (6.6%)	8 (17.8%)	0.039
Cerebrovascular disease	25 (15%)	14 (11.5%)	11 (24.4%)	0.037
Chronic renal failure	3 (1.8%)	2 (1.6%)	1 (2.2%)	1
Active malignancy	39 (23.4%)	23 (18.9%)	16 (35.6%)	0.024
Vital findings				
GCS score (median)	15 (15-15)	15 (15-15)	15 (12-15)	<0.01
GCS score (mean±std)	14.45±1.826	14.93±0.494	13.13±3.079	
Fever(median)	36.4 (36-38)	36.4 (36-36.7)	36.6 (36-37)	0.145
Fever (mean±std)	36.448±0.475	36.420±0.448	36.522±0.537	
Heart rate/min	100 (86-120)	100 (83-117)	110 (90-130)	0.008
Heart rate/min (mean±std)	103.75±24.4	100.25±23.036	113.24±25.704	
Respiratory rate/min	20 (18-24)	20 (18-22)	21 (17-25)	0.347
Respiratory rate/min (mean±std)	21.34±5.881	20.85±4.909	22.67±7.860	
Systolic TA	123 (103-144)	127 (110-155)	105 (92-130)	<0.001
Systolic TA (mean±std)	126.18±31.691	132.06±31.193	110.24±27.526	
Diastolic TA	74 (62-87)	78 (66-90)	70 (55-80)	0.004
Diastolic TA (mean±std)	74.69±18.053	77.20±17.603	67.91±17.693	
Saturation	90 (85-95)	91 (87-95)	87 (82-92)	0.001
Saturation(mean±std)	89.22±7.128	90.34±6.363	86.18±8.211	
G-PESI	30 (10-60)	30 (10-50)	60 (30-90)	<0.001
sPESI	2 (1-3)	2 (1-2)	2 (1-3)	0.006
sPESI risk classification				0.05
Low risk	16 (9.6%)	15 (12.3%)	1 (2.2%)	
High risk	151 (90.4%)	107 (87.7%)	44 (97.8%)	
PESI	113 (89-138)	106 (85-127)	132 (113-168)	<0.001
Outcome within the first 24 hours (n, %)				<0.001
Discharge	6 (3.6%)	6 (4.9%)	0	
Ward admission	110 (65.9%)	103 (84.4%)	7 (15.6%)	
Intensive care unit admission	51 (30.5%)	13 (10.7%)	38 (84.4%)	
Thrombolytic treatment (n, %)	13 (7.8%)	8 (6.6%)	5 (11.1%)	0.33
Length of hospital stay	7 (4-10)	7 (5-10)	5 (4-8)	0.117

GCS, Glasgow Coma Scale; PESI, pulmonary embolism severity index; G-PESI, geriatric pulmonary embolism severity index; sPESI, simplified pulmonary embolism severity index

According to the diagnostic test performance analysis report, the PESI, s-PESI, and G-PESI scores were statistically significant predictors of mortality, with AUC values of 0.736 (95% CIs 0.34–1.91), 0.635 (95% CIs 0.74–1.81), and 0.739 (95% CIs 0.50–2.18) at cutoff values of >110, >2, and >40, respectively (p<0.001, p<0.001, and p=0.004, respectively; **Table 2, Figure 1**) The AUC values of the PESI and G-PESI scores did not differ significantly (p=0.7241). Conversely, statistically significant differences were observed between the G-PESI and s-PESI (p=0.0029) and between the PESI and s-PESI (p=0.0015).

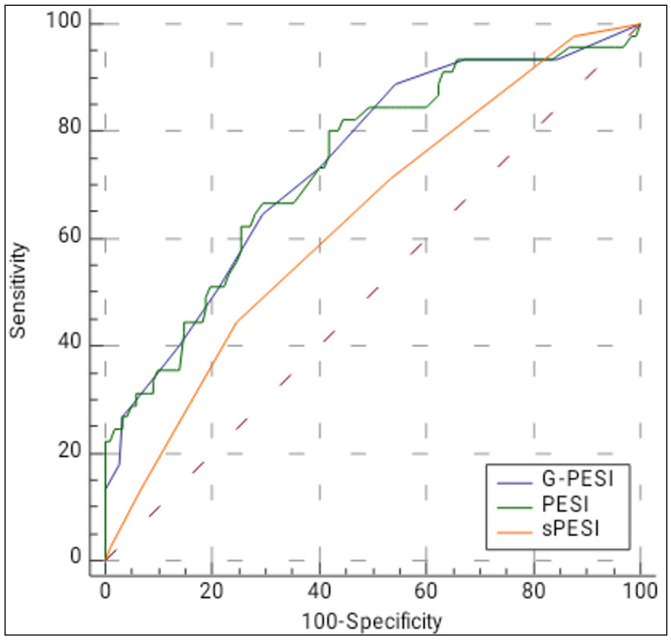

Figure 1. Receiver operating characteristic curves for the pulmonary embolism severity index (PESI), geriatric pulmonary embolism severity index (G-PESI), simplified pulmonary embolism severity index (sPESI) for the prediction of 30-day mortality in geriatric patients presenting to the emergency department with pulmonary embolism

The multivariate logistic regression analysis identified age, heart rate, and the GCS score as independent predictors of mortality (p=0.015, p=0.012, and p=0.003, respectively) (**Table 3**).

DISCUSSION

In this study, we designed a geriatric PESI and evaluated its ability to predict short-term mortality in geriatric patients presenting to the emergency department with pulmonary embolism. Our results indicate that the G-PESI is a promising short-term mortality predictor for these patients. Our results also show that the G-PESI and PESI could be used as independent risk predictors of geriatric pulmonary embolism. We performed a statistical analysis with nonparametric comparison tests to assess significant differences in G-PESI, PESI, and s-PESI scores between survivors and non-survivors. All three scores were significantly higher in the non-survivor group. In the discriminatory power analysis, we determined the AUC values of the G-PESI and PESI to be 0.739 and 0.736, respectively, which were good predictors according to the ROC curve analysis. On the other hand, the AUC value of the s-PESI was 0.635. This result suggests that only the G-PESI and PESI were good predictors of 30-day mortality in geriatric patients with pulmonary embolism. The AUC values of the G-PESI and PESI did not differ significantly. In addition, likelihood ratios (LRs) are the best way to determine the extent to which a scoring system can be used reliably (11-13). Positive (>5) and negative (<0.2) LRs provide the best idea. Based on this, we can state that the G-PESI, PESI, and s-PESI cannot be used clinically to predict short-term mortality in the emergency department since their LR values were neither >5 nor <0.2 on the other hand, multivariate logistic regression reinforced the idea

Table 2. Accuracy of the PESI, G-PESI, sPESI in predicting 30-day all-cause mortality

	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR-	Accuracy	95% CI	p-value
G-PESI	0.739	>40	64.44	70.49	44.6	84.3	2.18	0.50	34.94	66.6-80.4	<0.001
PESI	0.736	>110	80	58.20	41.4	88.7	1.91	0.34	38.20	66.2-80.1	<0.001
sPESI	0.635	>2	44.44	75.41	40	78.6	1.81	0.74	19.85	55.7-70.8	0.004

PESI, pulmonary embolism severity index; G-PESI, geriatric pulmonary embolism severity index; sPESI, simplified pulmonary embolism severity index; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR, Likelihood Ratio

Table 3. Multivariate analysis of the PESI parameters and the PESI, sPESI and G-PESI scores

	Univariate Analysis		Multivariate Analysis	
	OR (95% (CI)	p	OR (95% CI)	p
Age, years	-	0.823	0.72 (0.55-0.93	0.015
Age, ≥75 vs. <75	0.83 (0.41-1.64)	0.594		
Gender	-	0.342	0.76 (0.26-2.16)	0.610
PESI	-	<0.001	1.42 (1.09-1.87)	0.009
G-PESI	-	<0.001	0.73 (0.56-0.95)	0.019
sPESI	-	0.006	0.31 (0.14-0.68)	0.003
Heart rate (/min)	-	0.008	1.02 (1.00-1.05)	0.012
Systolic blood pressure (mmHg)	-	<0.001	0.98 (0.96-1.00)	0.079
Glasgow Coma Scale score	-	<0.001	0.43 (0.25-0.74)	0.003
Oxygen saturation (%)	-	0.001	0.95 (0.88-1.03)	0.294

CI, Confidence interval

that the G-PESI and PESI could be used as independent predictors of geriatric pulmonary embolism.

The PESI, developed by Aujesky et al. (6), is routinely used in the evaluation of pulmonary embolism and consists of 11 criteria, including laboratory parameters and examination findings. Evaluating 15,752 patients from 189 hospitals whose pulmonary disease severity ranged from the low-risk to the massive or even arrest-inducing type, Aujesky et al. (6) found that the PESI was a statistically significant predictor of prognosis and mortality. The authors concluded that this scoring system could help identify very low-risk and low-risk patients with pulmonary embolism to initiate outpatient treatment and achieve early discharge.

The s-PESI was introduced by Jimenez et al., who reduced the PESI criteria from 11 to 6 by removing, respiratory rate, fever, and mental impairment. The authors found that the PESI and s-PESI had similar prognostic values but the PESI was more accurate and reliable in identifying patients with a low risk of death than the s-PESI (7). A multicenter cohort study involving 1,715 patients with a mean age of 67 years found a significantly lower mortality rate among patients with an s-PESI score of 0 than among patients with a score of 1(14). A study comparing the s-PESI, PESI, and Geneva prognostic score found that all three scoring systems were effective in determining 30-day mortality among patients with low-risk pulmonary embolism (15). However, a multicenter study of 449 patients with pulmonary embolism aged over 65 years reported that the s-PESI and PESI were superior to the Geneva prognostic score in predicting a poor prognosis in patients diagnosed with low-risk pulmonary embolism. This was attributed to the absence of the age parameter in the Geneva prognostic score (16). In our study, we thought that the use of G-PESI instead of PESI would reduce the length of hospital stay. However, we found that there was no statistically significant difference between the length of hospital stay and mortality (p=0.117). Although the mortality relationship of comorbid diseases, which are both PESI and G-PESI criteria, was not statistically significant. Again, the correlations between heart rate, systolic blood pressure and oxygen saturation with mortality were statistically significant from both PESI and G-PESI criteria. This caused both PESI and G-PESI to be significantly associated with mortality. While there is no statistically significant relationship between age and mortality; age appeared as an independent risk factor. We did not include the age parameter in the G-PESI. We found that the effectiveness of the G-PESI in predicting mortality was comparable to that of the PESI. Moreover, we found that the PESI and G-PESI were superior to the s-PESI in this respect. Although age is seen as an independent risk factor, PESI could not be superior to G-PESI with the effect of other criteria, and removing the age criterion is as effective as PESI, which also includes the age criterion, in predicting the prognosis. Although we cannot say that G-PESI can be used instead of PESI, we can say that G-PESI is as effective as PESI in predicting mortality, even without age criteria.

Ostovan et al. (8) modified the s-PESI by replacing the "sat<90%" criterion with "$PaO_2/PaCO_2 \leq 1.8$"and adding the right ventricular strain parameter obtained from ECG. The authors found that the modified s-PESI was significantly associated with in-hospital and one-year mortality and had a higher AUC value than the original s-PESI. In our study, although there was a statistically significant relationship between low saturation and mortality, multivariate analysis revealed that saturation alone was not effective in predicting mortality. As an ECG finding, right ventricular strain was very rare, and the most common finding in both the entire patient sample and the non-survivor group was a normal sinus rhythm, followed by sinus tachycardia. The results were statistically significant (p=0.002). Furthermore, while there was a statistically significant relationship between mortality and the PESI parameters of low systolic blood pressure and increased heart rate and a low GCS score, we also found that heart rate and the GCS were independent predictors of mortality.

Limitations

In our article, we focused on the possibility of using PESI, which is used in the diagnosis of pulmonary embolism, without including age criteria. While patients over 65 years of age who were diagnosed with pulmonary embolism were included in the study; low-risk and high-risk patients could not be evaluated separately. Patients diagnosed with unilateral or bilateral pulmonary artery embolism and patients with partial or complete pulmonary artery occlusion could not be evaluated separately. Thus, our patient population was limited in number although it is a retrospective study in order to report the data in the best way possible.

CONCLUSION

In geriatric patients diagnosed with pulmonary embolism, G-PESI without age criteria can be used instead of PESI, which also includes age criteria. In addition, G-PESI was not superior to PESI in terms of predicting short-term mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ümraniye Education and Researches Hospital Clinical Research Ethics Committee (Date: 17.06.2021, Decision No: B.10.1.TKH.4.34.H.GP.0.01/191).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Roy PM, Douillet D, Penaloza A. Contemporary management of acute pulmonary embolism. Trends Cardiovasc Med 2021; 29; S1050-1738(21)00068-2.
2. den Exter PL, van Es J, Erkens PM, et al. Impact of delay in clinical presentation on the diagnostic management and prognosis of patients with suspected pulmonary embolism. Am J Respir Crit Care Med 2013; 187: 1369-73.
3. Le Gal G, Righini M, Roy PM, et al. Differential value of risk factors and clinical signs for diagnosing pulmonary embolism according to age. J Thromb Haemost 2005; 3: 2457-64.
4. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005; 365: 331-40.
5. Robert-Ebadi H, Righini M. Diagnosis and management of pulmonary embolism in the elderly. Eur J Int Med 2014; 25: 343-9.
6. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005; 172: 1041-6.
7. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010; 170: 1383-9.
8. Ostovan MA, Ghaffari S, Pourafkari L, et al. Modification of simplified pulmonary embolism severity index and its prognostic value in patients with acute pulmonary embolism. Heart Lung Circulation 2016; 25: 184-90.
9. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982; 143: 29-36.
10. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983; 148: 839-43.
11. Deeks JJ. Systematic reviews of evaluations of diagnostic and screening tests. In:Egger M Davey Smith G Altman DG (Eds). Systematic reviews in health care: meta-analysis in context. Systematic reviews. 2nd edition, BMJ Books London 2001, pp 248-82.
12. Price CP, Newall RG, Boyd JC. Use of protein: creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. Clin Chem 2005; 51: 1577-86.
13. Fischer JE, Bachmann LM, Jaeschke R. A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. Intensive Care Med 2003; 29: 1043-51.
14. Yamashita Y, Morimoto T, Amano H, et al. Validation of simplified PESI score for identification of low-risk patients with pulmonary embolism: From the COMMAND VTE Registry. Eur Heart J: Acute Cardiovasc Care 2020; 9: 262-70.
15. Jaquet E, Tritschler T, Stalder O, et al. Prediction of short-term prognosis in elderly patients with acute pulmonary embolism: validation of the RIETE score. J Thromb Haemost 2018; 16: 1313-20.
16. Zwierzina D, Limacher A, Méan M, et al. Prospective comparison of clinical prognostic scores in elder patients with a pulmonary embolism. J Thromb Haemost 2012; 10: 2270-6.

Original Article

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Diagnostic and prognostic value of the ratio of mean platelet volume to platelet count in acute mesenteric ischemia

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ABSTRACT

Introduction: Acute mesenteric ischemia (AMI) is a condition in which there is a sudden cessation of blood supply to a particular intestinal segment and consequent cellular damage. Although it has a low incidence of approximately 0.09-0.2% of all emergency surgery admissions, AMI is a severe condition that can cause high early mortality. A direct relationship between an increased mean platelet volume (MPV) and acute thrombotic events has been shown in recent years. we aimed to find out whether the diagnosis of mesenteric ischemia and the amount of bowel segment affected by ischemia will guide clinicians preoperatively with these markers

Material and Method: A total of 57 cases with bowel resection due to mesenteric ischemia were included in the study. The gender, age, serum platelet (PLT), MPV, white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), Albumin, CRP, neutrophil-lymphocyte ratio (NLR), MPV/Platelet Count, and CRP-albumin ratio (CAR) levels at the time of admission, operation time, length of resected bowel segment, length of hospital stay, presence of necrosis and perforation from pathology reports, and length of bowel segment leading to necrosis were scanned.

Results: A moderate (moderate) negative correlation was found between the length of resected bowel segment and PLT ($P<0.001$; $r=-0.685$). A moderate positive significant correlation was found between resection length and MPV ($P<0.001$; $r=0.565$). A high significant positive correlation was found between resection length and MPV/PC ($P<0.001$; $r=0.857$). PLT, WBC and MPV/PC values were statistically different between the perforated group and no-perforation group ($p=0.009$, $p=0.024$, $p=0.010$). WBC and MPV/PC values were significantly higher in the perforated group.

Conclusion: MPV/PC and PLT value at hospital admission is a reliable and simple predictive factor in determining perforation and the amount of bowel segment affected in patients with acute mesenteric ischemia.

Keywords: Acute mesenteric ischemia, mean platelet volume, platelet indices, bowel necrosis

INTRODUCTION

Acute mesenteric ischemia (AMI) is a condition in which there is a sudden cessation of blood supply to a particular intestinal segment and consequent cellular damage (1). Although it has a low incidence of approximately 0.09-0.2% of all emergency surgery admissions, AMI is a severe condition that can cause high early mortality. If early and effective intervention is not performed, the risk of mortality increases even more (2). Rapid, easily accessible, uncomplicated, person-independent methods are needed to diagnose AMI, usually due to non-specific clinical findings and diagnostic limitations. Early detection of AMI, particularly before signs of multi-organ failure or clinical peritonitis appear, reduces morbidity and mortality, improves patient outcomes, and reduces surgical complications (3,4).

Decreased mesenteric blood flow resulting from a sudden arterial occlusion results in reduced oxygen transport that cannot meet the metabolic needs of the visceral organs. However, the first response to this condition is vasodilation, the response changes in the direction of vasoconstriction in prolonged ischemia. Systemic inflammatory pathways are activated with mucosal and submucosal damage (5).

Although serum laboratory tests are predictive in diagnosing acute mesenteric ischemia, they are not helpful in the definitive diagnosis. There is a left shift in neutrophils in AMI, an increase in leukocytes and CRP. Still, these parameters are not specific as they are elevated in all inflammation and infectious diseases (6). Metabolic acidosis occurs in approximately half of the patients. In cases of necrosis, increased non-AMI-specific laboratory

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tests such as hyperamylasemia, prerenal azotemia, increased phosphate, and alkaline phosphatase levels are also seen (7). There are also studies evaluating the increase in lactate level as a marker showing ischemia (8). The number of studies focusing on investigating a specific biochemical and serological parameter in the early diagnosis of AMI has increased recently (9).

In AMI, excessive inflammation and infection have prompted researchers to investigate inflammation-related hemogram parameters. Among these, mean platelet volume (MPV) has been a parameter that has been emphasized in many studies (10). In the study of Türkoğlu A et al. (11), it was shown that a high MPV level was associated with AMI in patients who applied to the emergency department with abdominal pain. In addition, another study concluded that patients with high MPV had worse survival in mesenteric ischemia (12). MPV is an indicator of the size and activation of platelets, and high MPV levels reflect increased production and activation of platelets. An increase in MPV indicates increased production of large platelets. This is a harbinger of more enzymatic activity and high thrombogenic potential. These platelets are more active, and increased activity causes an increase in the expression of secreted molecules such as thromboxane A2 and p-selectin and adhesion molecules. This triggers binding to the endothelium (13). In light of this information, increased MPV rates in mesenteric ischemia patients are expected. A direct relationship has been shown between increased MPV and acute thrombotic events such as acute myocardial infarction, unstable angina, and stroke (14-16). In this study, we aimed to determine whether the diagnosis of mesenteric ischemia and the amount of bowel segment affected by ischemia will guide clinicians preoperatively with these markers. Ours is the first article investigating the relationship between biochemical markers and the intestinal segment affected in mesenteric ischemia to the best of our knowledge.

MATERIAL AND METHOD

Ethics committee approval of this study was received from Hitit University Non-interventional Researches Ethics Committee (Date: 27/09/2021, Decision No: 2021-78). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

For this study, a total of 317 cases were found by scanning all segmental and subtotal small bowel resections performed in Hitit University Department of General Surgery between 01.01.2016 and 15.05.2021. Among these cases, 81 patients remained after excluding cases that had resection due to oncological surgeries, incarcerated inguinal hernias, and other causes other than mesenteric ischemia. After examining the surgical notes and pathology reports of these 81 cases, it was observed that other intra-abdominal pathologies were found in 18 cases, and they were excluded from the study. Five more patients were excluded due to the presence of known hematological disease, and a total of 57 cases with bowel resection due to mesenteric ischemia were included in the study.

From the hospital information management system and patient files of 57 patients included in the study, the gender, age, serum platelet (PLT), MPV, white blood cell count(WBC), neutrophil count (NEU), lymphocyte count (LYM), Albumin, CRP, neutrophil-lymphocyte ratio (NLR), MPV/Platelet Count and CRP-albumin ratio (CAR) levels at the time of admission, operation time, length of resected bowel segment, length of hospital stay, presence of necrosis and perforation from pathology reports, and length of bowel segment leading to necrosis were scanned.

Statistical Analysis

Statistical analyzes of the data collected in our study were performed with the SPSS (SPSS Inc., Chicago, IL, USA) package program. Shapiro-Wilk test was used to determine whether the data obtained with the measurement were in accordance with the normal distribution. Descriptive statistics of continuous variables suitable for normal distribution were reported as mean ± standard deviation. Descriptive statistics for non-normally distributed data were presented as median ± interquartile range (IQR). Categorical variables were presented with frequency (n). Independent groups t-test for normally distributed data in comparison of patient age, operative time, hospital stay, platelet (PLT), MPV, white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), Albumin, CRP, neutrophil-lymphocyte ratio (NLR), MPV/Platelet Count and CRP-albumin ratio (CAR) values by perforation status, and for data not normally distributed Mann-Whitney U test was used. The data distribution analyzed the relationship between numerical variables using the Spearman correlation coefficient. ROC (Receiver Working Characteristic) analysis was used to determine whether PLT, MPV, WBC, NEU, LYM, Albumin, CRP, NLR, MPV/PC, and CAR values are prognostic indicators for perforation prediction. As a result of the ROC analysis, the area under the ROC curves (AUC) and the 95% confidence interval of this area were determined. The AUC values obtained from the analysis were 0.9-1: excellent, 0.8-0.9: good, 0.7-0.8: moderate, 0.6-0.7: poor, and 0.5-0, 6: evaluated as unsuccessful. The best cut-off point in the ROC analysis was determined by the Youden index (maximum sensitivity and selectivity). To determine the discriminating power of the parameters that can

be used to diagnose perforation, the cut-off points are determined after the ROC analysis. And the sensitivity, selectivity, positive-negative predictive values, and likelihood ratio (+) values were calculated. Univariate and Multivariate Binary Logistic Regression analyses were used to determine the risk factors in the formation of perforation. Odds ratios (OR) with 95% confidence intervals were calculated for each parameter found to be statistically significant in Logistic Regression analysis. Statistical significance level was accepted as p <0.05.

RESULTS

There were 57 patients in this study. Bowel perforation due to mesenteric ischemia was observed in 17.5% (n=10) of the cases, and perforation was not observed in 82.5% (n=47) of the patients. Twentythree (40.4%) patients were female, and 34 (59.6%) were male. The mean age of the patients in this study was 71.05±12.03 (48-97). The mean age of Group 1 (with bowel perforation) was 71.90±11.42 (50-91), and the mean age of Group 2 (without bowel perforation) was 70.87±12.26 (48-97). The age of the patients was not statistically different between the groups (p=0.809). The mean operation time of all patients was 110.42±27.96 (60-180). The operation times of Group 1 were 122.5±33.63 (75-180), and the operation times of Group 2 were 107.85±26.31 (60-169). Operation times were not statistically different between the groups (p=0.134). The mean hospital stay of all patients was 15.12±24.19 (1-181). The duration of hospitalization in the group with perforation was 17.20±15.82 (median±IQR: 8.5±30), and the duration of hospitalization in the group without perforation was 14.68±25.73 (median±IQR: 10±7). The patients' length of stay was not statistically different between the groups (p=0.760). The female-male ratios were not statistically different between the groups (p=0.178). In the perforated group, 20% (n=2) were female and 80% (n=8) male, 44.7% (n=21) female and 55.3% (n=26) male of the non-perforated group .

The correlation analysis results between the resected bowel segment length and PLT, MPV, WBC, NEU, LYM, Alb, CRP, NLR, MPV/PC, and CAR are given in Table 1. A moderate negative correlation was found between the length of resected bowel segment and PLT (P<0.001; r=-0.685). A moderate positive significant correlation was found between resection length and MPV (P<0.001; r=0.565). A high significant positive correlation was found between resection length and MPV/PC (P<0.001; r=0.857). A very weak (negligible) significant positive correlation was found between resection length and CAR (P=0.047; r=0.264). No significant correlation was found between the length of resected bowel segment and other blood values (P>0.05).

Table 1. Results of correlation analysis between resected bowel segment length and PLT, MPV, WBC, NEU, LYM, Alb, CRP, NLR, MPV/PC, and CAR (n=57)

		Length of resected bowel
PLT	r	-0.685**
	p	<0.001
MPV	r	0.565**
	p	<0.001
WBC	r	0.200
	p	0.136
NEU	r	0.133
	p	0.324
LYM	r	0.053
	p	0.696
Alb	r	-0.213
	p	0.112
CRP	r	0.231
	p	0.083
NLR	r	0.221
	p	0.099
MPV/PC	r	0.857**
	p	<0.001
CAR	r	0.264*
	p	0.047

Spearman correlation coefficient, PLT: platelets, MPV: Mean platelet volume, WBC: White blood cell count, NEU: Neutrophil, LYM: Lymphocyte, CRP: c-reactive protein, NLR: neutrophil to lymphocyte ratio, MPV/PC: Mean platelet volume to platelet count, CAR: c-reactive protein to albumin ratio

The comparison of PLT, MPV, WBC, NEU, LYM, Albumin, CRP, NLR, MPV/PC, CAR values of patients in Group 1 and Group 2 is presented in **Table 2**. PLT, WBC and MPV/PC values were statistically different between the groups (p=0.009, p=0.024, p=0.010 **Table 2**). WBC and MPV/PC values were significantly higher in the perforated group (**Table 2**). PLT values were significantly lower in the perforated group (**Table 2**). MPV, NEU, LYM, Albumin, CRP, NLR, and CAR values were not statistically different (P>0.05). Distribution is shown in **Figure 1.**

Table 2. Comparison of laboratory values, NLR, MPV/PC, and CAR values between groups

	Perforation		P values
	No (n=47)	Yes (n=10)	
PLT	254.6±64.80	192.6±70.23	0.009[a]
MPV	10.64±1.470	11.08±1.423	0.395[a]
WBC	12.86±6.460	18.23±7.55	0.024[a]
NEU	10±9.26	10.92±7.05	0.390[b]
LYM	0.99±1.03	1.32±0.81	0.450[b]
Albumin	3.14±0.717	2.82±0.763	0.215[a]
CRP	113±121.9	96±77.58	0.916[b]
NLR	10.23±12.52	9.82±10.99	0.629[b]
MPV/PC	0.042±0.018	0.068±0.030	0.010[b]
CAR	38.13±44.53	29.05±37.29	0.660[b]

a Student's t-test with mean ± standard deviation (SD), b Mann Whitney U test with median ± interquartile range (IQR), PLT: platelets, MPV: Mean platelet volume, WBC: White blood cell count, NEU: Neutrophil, LYM: Lymphocyte, CRP: c-reactive protein, NLR: neutrophil to lymphocyte ratio, MPV/PC: Mean platelet volume to platelet count, CAR: c-reactive protein to albumin ratio

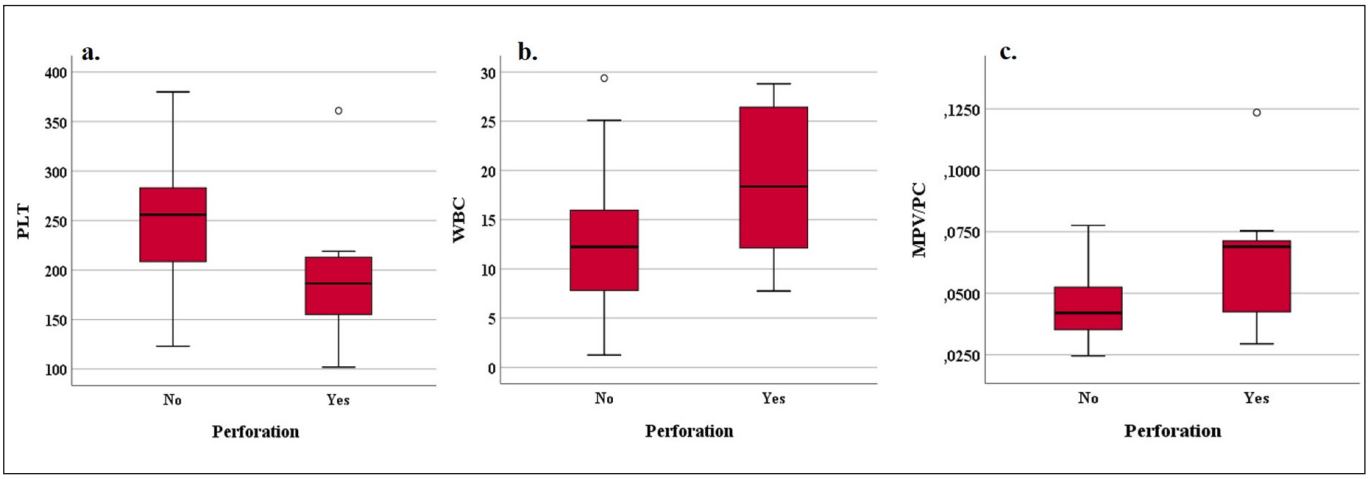

Figure 1. Boxplot of the distribution of (a.) PLT: platelets, (b.) WBC: White blood cell count and (c.) MPV/PC: Mean platelet volume to platelet count values among groups

As a result of blood parameters and ROC analysis for NLR, MPV/PC and CAR, MPV, WBC, NEU, LYM, Albumin, CRP, NLR and CAR parameters were insignificant in the differentiation of perforation (Respectively; AUC= 0.591; p=0.367, AUC=0.696; p=0.054, AUC=0.587; p=0.390, AUC=0.577; p=0.450, AUC=0.634; p=0.186, AUC=0.511; p=0.916, AUC= 0.549; p= 0.629, AUC=0.545; p= 0.660). As a result of ROC analysis, PLT and MPV/PC parameters were found to be significant in perforation discrimination (AUC=0.777 (0.606-0.947), p=0.006, AUC=0.762 (0.581-0.943), p=0.010 **Table 4**) The number of patients with successful categorization of the parameters in the prediction of perforation according to the cut-off values chosen as a result of the ROC analysis is shown in **Table 3** to determine the success of the PLT and MPV/PC values in the prediction of perforation.

In addition, the 95% confidence intervals were calculated as a result of the ROC analysis, together with the AUC values and the sensitivity, selectivity, positive-negative predictive values, and the likelihood ratio (+) values calculated using **Table 3** values, are presented in **Table 4.** The ROC curve is shown in **Figure 3**. The cut-off point for the PLT value was found to be 220.5. Classification success for this cut-off point; sensitivity was 90%, and selectivity was 72.3% (**Table 4**). The cut-off point for the MPV/PC value was found to be 0.066. Classification success for this cut-off point; sensitivity was 60%, and selectivity was 91.4% (**Table 4**).

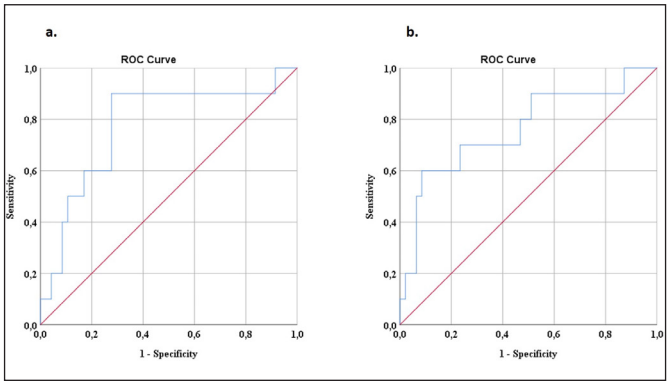

Figure 3. ROC curves for (a.) PLT: platelets, (b.) MPV/PC: Mean platelet volume to platelet count values in perforation prediction

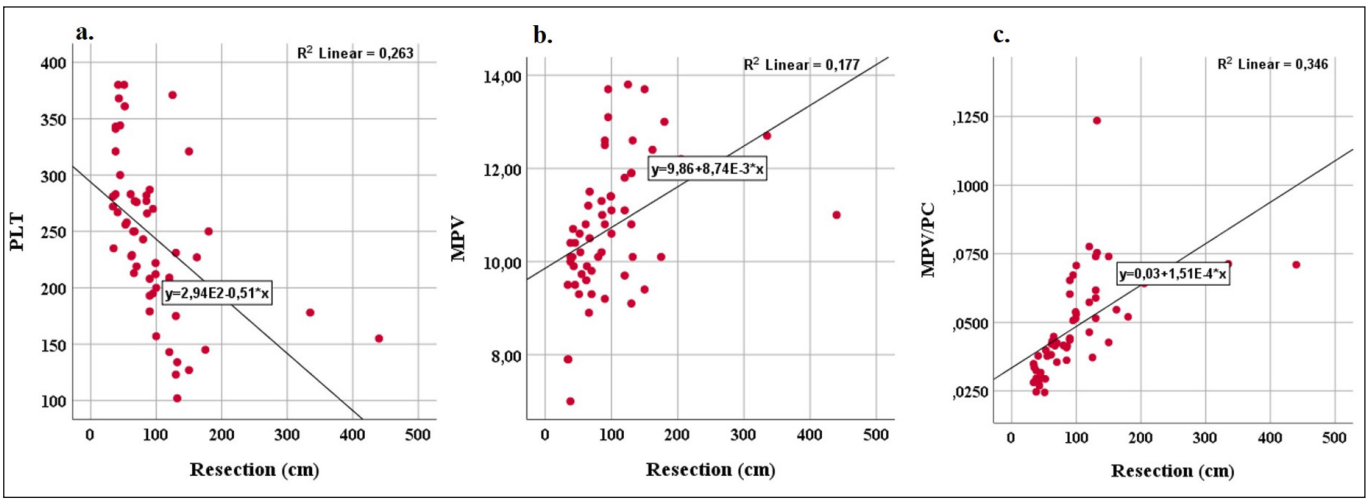

Figure 2. Scatter plot of the distribution of (a.) PLT: platelets, (b.) MPV: Mean platelet volume and (c.) MPV/PC: Mean platelet volume to platelet count values among resection

Table 3. The success of cut-off values determined by ROC analysis in perforation prediction

	Cut-off	Perforation		Total
		No	Yes	
PLT	> 220.5	34	1	35
	≤ 220.5	13	9	22
MPV/PC	< 0.066	43	4	47
	≥ 0.066	4	6	10
Total		47	10	57

PLT: platelets, MPV/PC: Mean platelet volume to platelet count

Table 4. Results of ROC analysis; and sensitivity, specificity, PPV, NPV, and likelihood ratio (+) values of PLT and MPV/PC values for prediction of perforation

	PLT	MPV/PC
AUC (95% CI)	0.777 (0.606-0.947)	0.762 (0.581-0.943)
P values	0.006	0.010
Cut off	≤ 220.5	≥ 0.066
Sensitivity (95% CI)	0.9 (0.541-0.994)	0.6 (0.273-0.863)
Specificity (95% CI)	0.723 (0.571-0.839)	0.914 (0.787-0.972)
PPV (95% CI)	0.409 (0.214-0.633)	0.6 (0.273-0.863)
NPV (95% CI)	0.971 (0.833-0.998)	0.914 (0.787-0.972)
LR+ (95% CI)	3.25 (1.96-5.39)	7.05 (2.42-20.45)

ROC: Receiver Operating Characteristic, PPV: positive predictive value, NPV: negative predictive value, AUC: Area under the curve, CI: Confidence interval
PLT: platelets, MPV/PC: Mean platelet volume to platelet count

Univariate and Multivariate Binary Logistic Regression analysis results were performed to determine the effective parameters in the formation of perforation, and the odds ratio (OR) and 95% confidence intervals for each statistically significant parameter are presented in **Table 5.** Gender and age were statistically insignificant in the univariate model (p=0.164, p=0.805, respectively; **Table 5**). The OR (95% CI) for PLT and MPV/PC were 23.53 (2.7-204.6) and 16.12 (3.16-82.1), respectively (p=0.004, p=0.001; **Table 5**). In the multivariate model, MPV/PC was statistically insignificant (p=0.105). The OR (95% CI) for the statistically significant PLT was 11.33 (1.04-122.3) (p=0.046; **Table 5**).

Table 5. Univariate and multivariate binary logistic regression analysis results

	Univariate		Multivariate	
	P values	OR (CI 95%)	P values	OR (CI 95%)
Gender	0.164	-	-	-
Age	0.805	-	-	-
PLT ≤ 220.5	0.004	23.53 (2.7-204.6)	0.046	11.33 (1.04-122.3)
MPV/PC ≥ 0.066	0.001	16.12 (3.16-82.1)	0.105	4.5 (0.73-27.73)
Multivariate model: Nagelkerke R Square=0.424, Classification accuracy: 86%				

OR: Odds ratio, CI: Confidence interval, PLT: platelets, MPV/PC: Mean platelet volume to platelet count, Reference value for PLT: > 220.5, Reference value for NLR: < 0.066

DISCUSSION

In our study, increased MPV and decreased platelet rates were found significant in the length of intestinal segment affected in mesenteric ischemia and acute mesenteric ischemia itself. However, according to this result, it would not be appropriate to think that "increased MPV proves to be a predictive value for perforation in acute mesenteric ischemia". Because AMI is not only a surgical but also a vascular disease, and high MPV can be found in atherosclerosis-related conditions. However, in addition to the values such as CRP, leukocytes, and CAR, which are routinely examined, we believe that the MPV/PC ratio is more significant than previous parameters in predicting perforation in mesenteric ischemia and in estimating the amount of affected bowel loop.

Many studies have investigated that NLR rate may be a precursor of acute mesenteric ischemia in patients with non-specific abdominal pain. In the Kısaoğlu A study (17), it was shown that NLR rates increased significantly when healthy individuals and AMI patients were compared, and it was argued that NLR is an independent prognostic factor in AMI patients. In our study, NLR parameters were insignificant in distinguishing perforation. This result was similar to WBC, NEU, LYM, Albumin, CRP, and CAR values. Although these values predict mesenteric ischemia, it seems more rational to use the MPV/PC ratio, which we also emphasized in our study, to predict perforation and can be used to estimate the length of a necrosed bowel segment.

In two separate studies with limb ischemia, low MPV values were found to be associated with critical lower limb ischemia and hepatic fibrosis(17-19). There are also studies that found decreased MPV levels in ulcerative colitis (20). These results are inconsistent with both ischemic cerebrovascular events, ischemic heart diseases, and high MPV results in mesenteric ischemic patients that we found in our study. Therefore, it was thought that this might be the severe systemic inflammatory response that occurs, especially in mesenteric ischemia.

In recent years, there has also been many researchs about platelet indices and cancer diagnosis, and cancer stage (21). Yang-Yang Wu et al. (22) found in their study about colorectal cancer MPV/PC was significantly different in subgroups between patients with stage I/II and stage III/IV cancer, and they believed that this ratio might be helpful in the differential diagnosis of early and advanced colorectal cancer.

Also, with the COVID-19 pandemic, coagulopathy-related diseases have been increased explicitly because there is growing evidence about SARS CoV-2 infection and hypercoagulability (23). Acute arterial obstruction of the small intestinal vessels and mesenteric ischemia may

appear due to hypercoagulability associated with SARS-CoV-2 infection, mucosal ischemia, viral dissemination, and endothelial cell invasion vis ACE-2 receptors (24). Serban D et al. (25) emphasized in their study that the diagnosis of an ischemic bowel should be one of the top differentials in critically ill patients with acute onset of abdominal pain and distension. So it is more than possible that we will encounter more patients with bowel ischemia than ever.

Our study concluded that the affected bowel length of patients who were operated on for mesenteric ischemia increased as the blood platelet value decreased and increased as the MPV, MPV/PC, and CAR values increased. Examination of these values, especially in patients before surgery, may help predict the amount of intestinal loop affected at the time of surgery.

This study has some limitations. Based on our results, several perspectives can be suggested. First, our study was a retrospective single-center study, and the cohort size may have limited the statistical power of the analysis. However, the number of patients per subgroup was sufficient to evaluate perforation discrimination and the amount of affected bowel loop according to laboratory parameters. Second, we investigated two parameters that influence the prognosis of mesenteric ischemia. It would be interesting to extend this study to larger cohorts and more extended follow-up periods. To the best of our knowledge, our study is the first to use laboratory data to predict perforation and the amount of affected bowel loop in case of mesenteric ischemia.

CONCLUSION

MPV/PC and PLT value at hospital admission is a simple and reliable predictive marker in determining perforation and the amount of bowel segment to be affected in patients with acute mesenteric ischemia. However, further studies are required to establish a causal link between MPV/PC and PLT values and patients' outcomes. It may be helpful as an inexpensive and non-invasive prognostic biomarker for centers without the possibility of computer tomography angiography, magnetic resonance angiography, etc.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval of this study was received from Hitit University Non-interventional Researches Ethics Committee (Date: 27/09/2021, Decision No: 2021-78).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Patel A, Kaleya RN, Sammartano RJ. Pathophysiology of mesenteric ischemia. Surg Clin North Am 1992; 72: 31-41.
2. Corcos O, Castier Y, Sibert A, et al. Effects of a multimodal management strategy for acute mesenteric ischemia on survival and intestinal failure. Clin Gastroenterol Hepatol 2013; 11: 158-65 e2.
3. Canfora A, Ferronetti A, Marte G, et al. Predictive factors of intestinal necrosis in acute mesenteric ischemia. Open Med (Wars) 2019; 14: 883-9.
4. Ichiba T, Hara M, Yunoki K, et al. Baseline disease is a more important predictor of intestinal necrosis than CT findings in patients with acute mesenteric ischemia. Am J Emerg Med 2016; 34: 2261-5.
5. Clair DG, Beach JM. Mesenteric Ischemia. N Engl J Med 2016; 374: 959-68.
6. Eldrup-Jorgensen J, Hawkins RE, Bredenberg CE. Abdominal vascular catastrophes. Surg Clin North Am 1997; 77: 1305-20.
7. Tsai CJ, Kuo YC, Chen PC, et al. The spectrum of acute intestinal vascular failure: a collective review of 43 cases in Taiwan. Br J Clin Pract 1990; 44: 603-8.
8. Sahin M, Bulus H, Yavuz A, et al. The role of the lactate level in determining the risk rates of small bowel resection in incarcerated hernias. Ulus Travma Acil Cerrahi Derg 2020; 26: 593-9.
9. Augene E, Lareyre F, Chikande J, et al. Platelet to lymphocyte ratio as a predictive factor of 30-day mortality in patients with acute mesenteric ischemia. PLoS One 2019; 14: e0219763.
10. Kantekin B, Avcil M, Kapçı M, et al. Are the blood urea nitrogen/creatinine ratio and the mean platelet volume able to act as predictors of mortality and morbidity in patients with upper gastrointestinal bleeding?. Anatolian Curr Med J 2021; 3: 274-8.
11. Türkoğlu A, Gül M, Oğuz A, et al. Mean platelet volume: is it a predictive parameter in diagnosis of acute mesenteric ischemia? Int Surg 2015; 100: 962-5.
12. Altintoprak F, Arslan Y, Yalkin O, et al. Mean platelet volume as a potential prognostic marker in patients with acute mesenteric ischemia-retrospective study. World J Emerg Surg 2013; 8: 49.
13. Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. Eur Heart J 2001; 22: 1561-71.
14. Amraotkar AR, Song DD, Otero D, et al. Platelet count and mean platelet volume at the time of and after acute myocardial infarction. Clin Appl Thromb Hemost 2017; 23: 1052-9.
15. Wasilewski J, Desperak P, Hawranek M, et al. Prognostic implications of mean platelet volume on short- and long-term outcomes among patients with non-ST-segment elevation myocardial infarction treated with percutaneous coronary intervention: A single-center large observational study. Platelets 2016; 27: 452-8.
16. Sabença F, Carvalho A, Rocha M, et al. Mean platelet volume and mechanical thrombectomy. J Stroke Cerebrovasc Dis 2020; 29: 104971.
17. Rief P, Raggam RB, Avian A, et al. Low mean platelet volume is associated with critical limb ischemia in peripheral arterial occlusive disease. Sci Rep 2018; 8: 6718.

18. Rachmanadi MB, Ismail MT, Anggraeni VY. Relationship between mean platelet volume and critical limb ischemia in diabetes mellitus patients. Int J Angiol 2021; 30: 257-61.
19. Akar M. Is mean platelet volume better than other long-used non-invasive parameters in assessing severe fibrosis in patients with chronic hepatitis B?. J Health Sci Med 2021; 4: 96-102.
20. Kamış F, Çetin E, Ugar M, et al. Ülseratif kolitte hastalık aktivitesini değerlendirmede ortalama trombosit hacmi ile nötrofil-lenfosit oranı ve platelet-lenfosit oranlarının değerlendirilmesi. J Med Palliat Care 2020; 1: 28-33.
21. Turhan VB, Ünsal A, Gök HF, et al. Predictive value of preoperative neutrophil-lymphocyte and platelet-lymphocyte ratio in determining the stage of colon tumors. Cureus 2021; 13: e18381.
22. Wu YY, Zhang X, Qin YY, Qin JQ, Lin FQ. Mean platelet volume/platelet count ratio in colorectal cancer: a retrospective clinical study. BMC Cancer 2019; 19: 314.
23. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020; 18: 1738-2.
24. Yantiss RK, Qin L, He B, et al. Intestinal abnormalities in patients with SARS-CoV-2 infection: histopathologic changes reflect mechanisms of disease. Am J Surg Pathol 2022; 46: 89-96.
25. Serban D, Tribus LC, Vancea G, et al. Acute mesenteric ischemia in COVID-19 Patients. J Clin Med 2021; 11: 200.

Original Article

HEALTH SCIENCES
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Evaluation of spleen stiffness in healthy population: a vibration-controlled transient elastography study

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ABSTRACT

Aim: Vibration-controlled transient elastography (VCTE) is an accurate technique that has an increasing use. In recent years, VCTE was started to use in predicting spleen stiffness (SS). Portal vein pressure and flow have an impact on SS and in previous studies it was used to predict portal hypertension, esophageal varices. In this study, our aim was to evaluate the SS measurements in healthy population and its correlation with age, sex, liver stiffness measurement (LSM), continued attenuation parameter (CAP) and body mass index (BMI).

Material and Method: We enrolled healthy volunteers who were agreed to participate to the study and collected age, sex, smoking history, alcohol consumption, body mass index before the VCTE procedure. Liver and spleen elastography were performed to all patients by VCTE.

Results: A total of 97 participants were enrolled to the study, 15 patients were excluded and 82 patients included for the final analysis. There was no significant difference in SS, liver stiffness measurement LSM, CAP and BMI between females and males. There was no correlation between age and SS. There was a weak correlation between SS and LSM, SS and CAP and no correlation was found between SS and BMI.

Conclusions: SS had a weak correlation with LSM and CAP but not with BMI, age and sex. There is no extra-large probe use in SS measurement and it was a challenge in participants with increased submucosal fat thickness. Multiple and repeatable studies needed to set an accurate cut-off point and evaluate the factors that impact on SS in healthy individuals.

Keywords: Liver stiffness; Spleen stiffness; Vibration-controlled transient elastography

INTRODUCTION

Non-invasive diagnosing techniques have an important role with the advances in technology. Eventually, the use of non-invasive technology in diagnostic modalities increasing rapidly. Vibration-controlled transient elastography (VCTE) is an accurate technique that has an increasing use in recent decade. VCTE uses share wave imaging to predict liver stiffness and does not need an ultrasound guidance prior to examination. This technique was accurately predicted the liver stiffness such as advanced fibrosis, cirrhosis, and distinguishing cirrhosis in patients with portal hypertension (1-3).

In recent years, VCTE was started to use in predicting spleen stiffness (SS). It could be affected from chronic fibrosis and could be affected from the splenic blood flow. Portal vein pressure and flow have an impact on SS and in previous studies it was used to predict portal hypertension, esophageal varices (4-6).

Normal and abnormal values and cut-off points of VCTE measurement are not clear in healthy population. It is important to differentiate safe and impaired results. Even predicting a disease is important by VCTE, excluding the heathy population is also important for clinician. Evaluating healthy population is crucial to set accurate cut-off points and affecting factors with multiple and repeatable studies.

In this study, our aim was to evaluate the SS measurements in healthy population and its correlation with other factors.

MATERIAL AND METHOD

This cross-sectional observational single-center study was conducted out at Marmara University, School of Medicine, Department of Gastroenterology out-patient clinic. The study was approved by the Marmara

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University Clinical Research Ethics Committee (Date: 06.11.2020, Decision No: 09.2020.1210). and the Helsinki Declaration guidelines were followed throughout the study. Written informed consent was obtained from all participants prior to the study.

We enrolled healthy volunteers who were agreed to participate to the study. Age under 18 years old, history of major clinical illness, pregnancy, ineffective spleen stiffness measurement was excluded from the study. We collected age, sex, smoking history, alcohol consumption, body mass index before the VCTE procedure.

Liver and spleen elastography were performed to all patients by FibroScan Expert 630 (Echosens, Paris France) with a concurrent ultrasound examination before the spleen stiffness measurement (7, 8). VCTE was performed by a trained and experienced physician (> 200 procedures) following an 8-hours fasting without any caffeine intake. Medium and x-large probes were used according to the patient's subcutaneous fat thickness. Liver stiffness measurement procedure was performed on the right lobe of the liver through the intercostal area. Spleen stiffness procedure was performed through the left intercostal area in supine position. Following confirming spleen with transabdominal ultrasonography, we put the SS meausrement probe on the previously confirmed area through the intercostal space and performed the measurement (9, 10). The physician performed at least 10 LS and SS measurements for each patient. We included the results with at least 10 valid measurements, a success rate above 60% were included to the study (11).

Normally distributed data will be expressed as mean±standard deviation, and the non-normal distributed data was expressed with the median values. Chi-square was used to test the difference between categorical variables and student's t-test or the Mann-Whitney U test was used to test the difference between continuous variables. The Spearman's rank correlation coefficient was used to measure the linear relationship between SS and age, body mass index (BMI), liver stiffness measurement (LSM) and continued attenuation parameter (CAP). p value < 0.05 accepted as significant.

RESULTS

A total of 97 participants were enrolled to the study. SS could not measure duo to the obesity and increased subcutaneous fat thickness in fifteen participants and they excluded from the study. Mean age was 37.80±11.13 years, 49 (59.8%) were female. Thirty-eight (46.3%) patients had alcohol consumption and 49 (59.8%) were non-smoker. The mean BMI was 26.67±5.12 kg/m² (**Table 1**).

Table 1. General characteristics of the participants

	All Patients (n=82)
Sex	
Female (n/%)	49 (59.8%)
Male (n/%)	33 (40.2%)
Age (years) (mean±SD)	37.80±11.13
BMI (kg/m²) (mean±SD)	26.67±5.12
Tobacco use (n/%)	
Current smoker	16 (19.5%)
Ex-smoker	17 (20.7%)
Non-smoker	49 (59.8%)
Alcohol consumption (n/%)	38 (46.3%)
LSM (kPa) (median, min-max)	4.40 (2.10-75.00)
CAP (dB/m) (mean±SD)	231.78±51.93
SS (n/%)	18.35 (7.20-80.10)

BMI: Body mass index; CAP: Continued attenuation parameter, LSM: Liver stiffness measurement; SS: Spleen stiffness, Data are presented as means and SD, counts, or medians and interquartile ranges, as appropriate.

There was no significant difference in SS [18.2 (range: 10.5-40.1) vs 18.9 (range: 7.2-80.1)] and LSM [4.4 (range:2.1-12.0) vs 4.4 (range: 2.5-75.0)] between females and males (p=0.891 and 0.925 respectively). Also, there was no significant difference in CAP values between females and males (226.06±56.24 vs 240.27 44.24, p =0.205). BMI was also similar in both females and males (26.48±5.64 vs 26.95±4.29, p=0.668).

The median age was 36 years. When we divide the cohort into two groups with a cut-off age of 36, there was no difference was seen in SS between older and youngers [17.8 (range:10.5-39.1 and 19.1 (range: 7.2-80.1), p =0.361]. Also, there was no correlation between age and SS (p=0.273).

Liver stiffness has a weak correlation with SS (0.388, p < 0.0001). When we evaluate the correlation between SS and CAP, there is also a weak correlation was found between two variables (r: 0.226, p=0.041). However, there was no correlation was found between SS and BMI (p=0.828) (**Figure 1**).

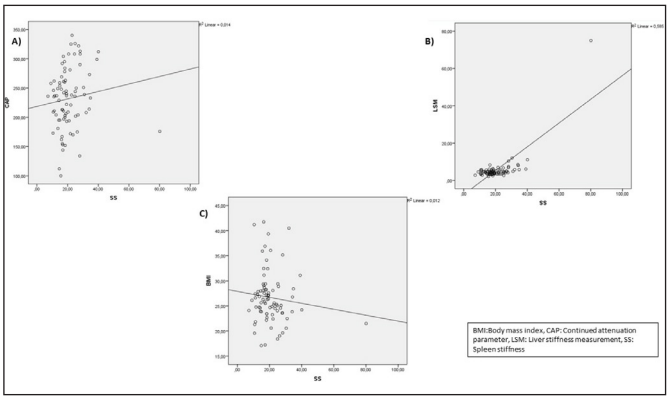

Figure 1. The Spearman's correlation between body mass index, continued attenuation parameter, liver stiffness measurement and spleen stiffness.

DISCUSSION

In our study, we found a positive significant correlation between SS and CAP and also between SS and LSM. On the other hand, there was no correlation was found between SS and BMI. There was no difference was found between male and females in SS, and there was no correlation was found between SS and age. We could not measure SS in 15 participants duo to obesity or increased subcutaneous fat thickness and excluded from the study. There is only medium probe available in spleen stiffness and SS could not be measured in especially participants with increased subcutaneous fat thickness.

In a previous that was similarly conducted with healthy controls, there was no relation was found between SS and BMI, age and sex and it is also similar with our study (12). In another healthy control study, there was no correlation was found between SS and age, SS and sex (13). In another study that was conducted with share wave elastography, there was no correlation was found between SS and age, also SS and BMI (14). Our result is in light with the current literature and there is no correlation of SS with BMI, age and sex.

In a study which was evaluated SS in chronic hepatitis C patients, there was a correlation was found with LSM (15). Also, in another study in hepatitis C, SS was found significantly higher in patients with F2 and F3 when compared with patients with F1 and F2 which was also evaluated with TE (16). We found a positive but wear correlation between LSM and SS in healthy controls and this result is similar with previous studies.

The absence of anatomic values of spleen such as spleen volume and diameter were limitations of our study. However, absence of portal venous pressure and diameter values was also a limitation. Single operator was an advantage to prevent bias on measurements. On the other hand, inter-observer evaluation could be a valuable information for the accuracy and may be a limitation at the same time.

CONCLUSION

SS was in correlation with LSM and CAP but not with BMI, age and sex. There is no extra-large probe use in SS measurement and it was a challenge in participants with increased submucosal fat thickness. Multiple and repeatable studies needed to set an accurate cut-off point and evaluate the factors that impact on SS in healthy individuals.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Marmara University Clinical Research Ethics Committee (Date: 06.11.2020, Decision No: 09.2020.1210).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Aykut UE, Akyuz U, Yesil A, et al. A comparison of FibroMeter™ NAFLD Score, NAFLD fibrosis score, and transient elastography as noninvasive diagnostic tools for hepatic fibrosis in patients with biopsy-proven non-alcoholic fatty liver disease. Scand J Gastroenterol 2014; 49: 1343-8.
2. Ziol M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005; 41: 48-54.
3. Sasso M, Beaugrand M, de Ledinghen V, et al. Controlled attenuation parameter (CAP): a novel VCTE™ guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol 2010; 36: 1825-35.
4. Hu X, Huang X, Hou J, Ding L, Su C, Meng F. Diagnostic accuracy of spleen stiffness to evaluate portal hypertension and esophageal varices in chronic liver disease: a systematic review and meta-analysis. Eur Radiol 2021; 31: 2392-404.
5. Reiberger T. The value of liver and spleen stiffness for evaluation of portal hypertension in compensated cirrhosis. Hepatol Commun 2021.
6. Mazur R, Celmer M, Silicki J, Hołownia D, Pozowski P, Międzybrodzki K. Clinical applications of spleen ultrasound elastography-a review. J Ultrason 2018; 18: 37-41.
7. Yilmaz Y, Ergelen R, Akin H, Imeryuz N. Noninvasive detection of hepatic steatosis in patients without ultrasonographic evidence of fatty liver using the controlled attenuation parameter evaluated with transient elastography. Eur J Gastroenterol Hepatol 2013; 25: 1330-4.
8. Yilmaz Y, Yesil A, Gerin F, et al. Detection of hepatic steatosis using the controlled attenuation parameter: a comparative study with liver biopsy. Scand J Gastroenterol 2014; 49: 611-6.
9. Bastard C, Miette V, Calès P, Stefanescu H, Festi D, Sandrin L. A novel FibroScan examination dedicated to spleen stiffness measurement. Ultrasound Med Biol 2018; 44: 1616-26.
10. Stefanescu H, Marasco G, Calès P, et al. A novel spleen-dedicated stiffness measurement by FibroScan® improves the screening of high-risk oesophageal varices. Liver Int 2020; 40: 175-85.
11. Boursier J, Zarski J-P, de Ledinghen V, et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology 2013; 57: 1182-91.

12. Giuffrè M, Macor D, Masutti F, et al. Evaluation of spleen stiffness in healthy volunteers using point shear wave elastography. Ann Hepatol 2019; 18: 736-41.
13. Pawluś A, Inglot MS, Szymańska K, et al. Shear wave elastography of the spleen: evaluation of spleen stiffness in healthy volunteers. Abdominal Radiol 2016; 41: 2169-74.
14. Albayrak E, Server S. The relationship of spleen stiffness value measured by shear wave elastography with age, gender, and spleen size in healthy volunteers. J Med Ultrasonics 2019; 46: 195-9.
15. Fraquelli M, Giunta M, Pozzi R, et al. Feasibility and reproducibility of spleen transient elastography and its role in combination with liver transient elastography for predicting the severity of chronic viral hepatitis. J Viral Hepat 2014; 21: 90-8.
16. Rewisha E, Elsabaawy M, Alsebaey A, et al. Evaluation of the role of liver and splenic transient elastography in chronic hepatitis c related fibrosis. J Liver: Dis Transplant 2016; 5.

Original Article

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Evaluation of the health literacy level of the patients who applied to a tertiary hospital family medicine clinic

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ABSTRACT

Aim: This study aimed to reveal the level of health literacy of the patients who applied to the family medicine clinic of a tertiary hospital in Turkey and its relationship with demographic parameters.

Material and Method: This study is a cross-sectional descriptive study. Study conducted in the family medicine clinic of an education hospital. Demographic characteristics and health literacy levels of the participants such as age, gender, marital status, educational status, professions, and financial status were noted. The health literacy levels of the participants were determined by using the Turkish Health Literacy Scale-32.

Results: A total of 443 participants were included in the study. the median age of the participants was 36. The median health literacy of the participants was 33.9 (25th and 75th quartiles: 29.2-40.8). The health literacy index of 57 (12.9%) participants were inadequate 139 (31.4%) participants was problematic, 147 (33.2%) participants were sufficient, and 100 (22.6%) participants was excellent. There was a statistically significant, negative, and weak correlation between age and health literacy index. (r=-0.200, p=0.01, Spearman correlation test).

Conclusion: Low health literacy is an important public health problem. Health literacy can be considered a priority policy issue. Legal arrangements can be made to carry out activities for health literacy.

Keywords: Health education, public policy, health literacy

INTRODUCTION

Although health literacy was first defined in 1974, the content and definition of this concept has changed over time (1,2). Currently, the World Health Organization describes health literacy as "the level of access, understanding and use of relevant information resources in order to make decisions on health services, protect, maintain and improve health, and improve the quality of life". On the other hand, the American Medical Association, describes health literacy as “individuals being able to read health-related messages, read and understand medicine boxes, and understand and do what is said by healthcare professionals” (2).

The first large-scale research in Turkey was carried out by the Health and Social Service Workers Union in 2014 (3). Another validity study in our country is the “Reliability and Validity Study of Health Literacy Scales in Turkey” conducted in 2016 with a large team under the editorship of Okyay and Abacıgil (4), with the contribution of Turkish Ministry of Health. In this study, health literacy scales for Turkish society were defined and validated. After the publication of this study, researchers in Turkey used these scales to evaluate and discuss the health literacy of the Turkish population in different cohorts (5).

In our study, we aimed to reveal the level of health literacy of the patients who applied to the family medicine clinic of a tertiary hospital in Turkey and its relationship with demographic parameters.

MATERIAL AND METHOD

This study approved by Clinical Research Ethics Committee of Ümraniye Training and Research Hospital (Date: 30.09.2021, Decision no: B.10.1.TKH.4.34.H.GP.0.01/285). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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It was planned as a cross-sectional descriptive study and conducted in the Ümraniye Training and Research Hospital Family Medicine Clinic. In this center, there are an average of 150 patient applications per day in 3 family medicine units. The study group consisted of individuals over the age of 18 who applied to the Family Health Center between October 10, 2021, and November 25, 2021, to receive health services, had no communication problems and could speak and understand Turkish, and agreed to participate in the study. Prior to the research application, the permission of the local clinical research ethics committee was obtained. Sampling was done every day of the week in order to increase the representativeness of the study group. To ensure random sampling, every four patients after the first randomly selected participant were offered to participate in the study.

Study form and informed consent form were prepared for the study. The informed consent form was signed by the participants who agreed to participate in the study. The study form was prepared to determine the demographic characteristics and health literacy levels of the participants such as age, gender, professions, educational status, marital status, and financial status. Educational status was recorded as primary and non-educated, secondary school, vocational high school, high school, university, master's degree, and doctorate. According to their professions, they were grouped as housewife, student, retired, tradesman, worker, self-employed, farmer and other. Participants were divided into subgroups according to their financial status as income more than expenses, income less than expenses and equal to income expenses.

The health literacy levels of the participants were determined by using the Turkish Health Literacy Scale-32 (TSOY-32) (4). In the light of the experiences gained in the Health Literacy Scale Development Workshop and the study of Reliability and Validity Study of Health Literacy Scales in Turkey, a change was made in the conceptual framework for the new likert scale. In Turkey, it was decided to combine the dimensions of "protection from diseases" and "promotion of health" of the conceptual framework and evaluate them together. For this purpose, a 32-item likert scale was developed by using the items suggested in the workshop. Unlike the original scale, TSOY-32 is structured as a 2X4 matrix by taking two basic dimensions, not three. Accordingly, the matrix consists of eight components: two dimensions (Treatment and service and prevention of diseases/health promotion) and four processes (accessing health-related information, understanding health-related information, evaluating health-related information, using/applying health-related information).

The interview participants were interviewed by a trained research assistant in the family medicine clinic, who read aloud the scale questions and answer options. Globally, health literacy indexes are standardized to be between 0 and 50. By using the index=(mean-1) x (50/3) formula, the index value was ensured to be between 0 and 50. Participants group as inadequate, problematic, sufficient, and excellent according to health literacy index. A score of 0-25 from the scale is defined as inadequate, a score of 25-33 is defined as problematic, a score of 33-42 is defined as sufficient, and a score of 42-50 is defined as excellent health literacy (4).

Jamovi version 0.9.6 program was used for statistical analysis. Categorical data were shown as n and percentage. Numerical data are shown with medians and quartiles of 25 and 75. Normality was evaluated with the Shapiro-Wilk test. The relationship between categorical data and health literacy was evaluated using the chi square test. The relationship between age and health literacy was evaluated using Spearman correlation. Values of 0.5 and above were used for the significant p value.

RESULTS

A total of 443 participants were included in the study. The median age of the participants was 36 (25^{th} and 75^{th} quartiles: 25-45). Two hundred and twenty-five (57.6%) of the participants were female. The median health literacy of the participants was 33.9 (25^{th} and 75th quartiles: 29.2-40.8). The health literacy index of 57 (12.9%) participants was inadequate and 100 (22.6%) participants were excellent. The demographic and descriptive characteristics of the participants and the health literacy index distribution are shown in **Table 1**. The health literacy index distribution is shown in **Figure 1**.

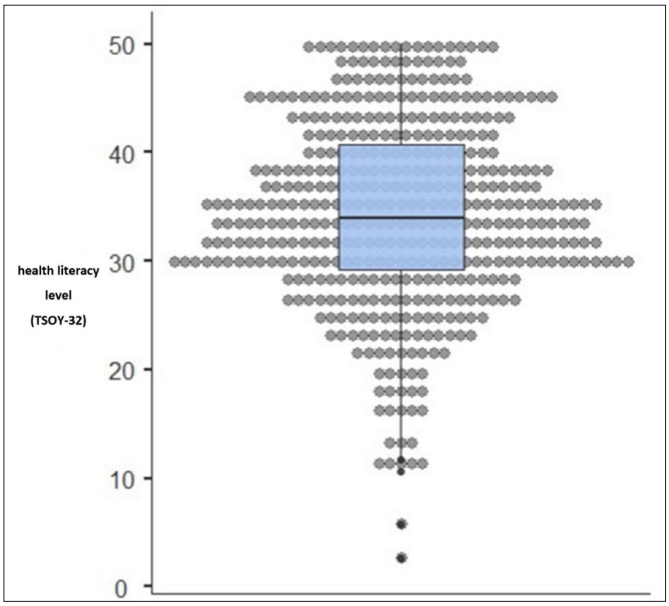

Figure 1. The health literacy index distribution (box plot and stacked data)

Table 1. The demographic and descriptive characteristics of the participants and the health literacy index distribution

n=443	n	%
Gender		
Male	188	42.4
Female	255	57.6
Marital status		
Married	285	64.3
Single	158	35.7
Educational Status		
Primary and non-educated	98	22.1
Secondary school	83	18.7
Vocational high School	23	5.2
High school	144	32.5
University	82	18.5
Master's degree	10	2.3
Doctorate	3	0.7
Professions		
Housewives	114	25.7
Students	48	10.8
Retirees	22	5
Artisans	13	2.9
Workers	106	23.9
Freelancers	41	9.3
Farmers	4	0.9
Others	56	12.6
Financial status		
Income less than expense	180	40.6
Income equivalent	217	49
Income more than expense	46	10.4
Health literacy index		
Inadequate	57	12.9
Problematic	139	31.4
Sufficient	147	33.2
Excellent	100	22.6

Data of the comparison of categorical data and health literacy index are presented in **Table 2**. The relationship between health literacy index and categorical data by using univariant tests. The difference between the categorical groups was not statistically significant. Except for financial status, there was no statistically significant relationship between the categorical groups and the health literacy index. The p values were 0.136, 0.097, 0.161, 0.664, and 0.042 for gender, marital status, educational status, professions, and financial status, respectively (chi square test). There was a statistically significant, negative, and weak correlation between age and health literacy index. (r=-0.200, p=0.01, Spearman correlation test).

DISCUSSION

Health literacy, which is one of the emerging current public health problems all over the world, is gaining importance in Turkey as well. Regarding the subject, health care in Turkey as well as in developed countries. Studies that reveal the situation regarding literacy and the factors affecting it have begun to be carried out in Turkey as well (5).

In this study we evaluated level of health literacy of the patients who applied to the family medicine clinic of a tertiary hospital in Turkey. The results of our study revealed that 44.3% of our cohort had inadequate or problematic health literacy levels. The health literacy median score in the study was determined as 33.9. To the

Table 2. The comparison of health literacy index and categorical data

n=443	Inadequate n=57	Problematic n=139	Sufficient n=147	Excellent n=100	P*	Median (25th -75th percentiles)	P**
Gender					0.429		0.136
Male	23 (12.2%)	66 (35.1%)	62 (33%)	37 (19.7%)		33.3 (28.8-39.7)	
Female	34 (13.3%)	73 (28.6%)	85 (33.3%)	63 (24.7%)		34.4 (29.7-41.8)	
Marital status					0.095		0.097
Married	37 (13%)	100 (35.1%)	85 (29.8%)	63 (22.1%)		33.3 (28.6-40.3)	
Single	20 (12.7%)	39 (24.7%)	62 (39.2%)	37 (23.4%)		35.1 (29.9-41.8)	
Educational Status					0.123		0.161
Primary and non-educated	16 (16.3%)	30 (30.6%)	32 (32.7%)	20 (20.4%)		33.3 (27.6-39.3)	
Secondary school	16 (19.3%)	26 (31.3%)	20 (24.1%)	21 (25.3%)		32.8 (27.9-42.0)	
Vocational high School	0	10 (43.5%)	9 (39.1%)	4 (17.4%)		34.9 (31.1-37.5)	
High school	19 (13.2%)	40 (27.8%)	49 (34%)	36 (25%)		34.1 (29.7-42)	
University	4 (4.9%)	28 (34.1%)	32 (39%)	18 (22%)		34.9 (30.1-40.5)	
Master's degree	2 (20%)	4 (40%)	3 (30%)	1 (10%)		30.5 (28.5-34.1)	
Doctorate	0	1 (33.3%)	2 (67%9	0		34.4 (32.3-37)	
Professions					0.080		0.664
Housewives	15 (13.2%)	40 (35.1%)	33 (28.9%)	26 (22.8%)		33.3 (29.6-41)	
Students	7 (14.6%)	6 (12.5%)	20 (41.7%)	15 (33.1%)		37.8 (32.7-43.7)	
Retirees	3 (13.6%)	9 (40.9%)	4 (18.2%)	6 (27.3%)		34.4 (29.3-41)	
Artisans	4 (30.8%)	8 (61.5%)	0	1 (7.7%)		29.2 (24.4-30.2)	
Workers	15 (14.2%)	24 (22.6%)	43 (40.6%)	24 (22.6%)		32.3 (29-39.6)	
Freelancers	3 (7.3%)	13 (31.7%)	14 (34.1%)	11 (26.8%)		34.4 (29.2-42.7)	
Farmers	2 (50%)	1 (25%)	1 (25%)	0		26 (23-29.8)	
Others	6 (10.7%)	19 (33.9%)	22 (39.3%)	9 (16.1%)		33.8 (30.1-39.2)	
Financial status					0.157		0.042
Income less than expense	29 (16.1%)	58 (32.2%)	60 (33.3%)	33 (18.3%)		33.3 (28.1-39.3)	
Income equivalent	24 (11.1%)	71 (32.7%)	66 (30.4%)	56 (25.8%)		34.4 (29.2-39.3)	
Income more than expense	4 (8.7%)	10 (21.7%)	21 (45.7%)	11 (23.9%)		35.2 (31.9-39.1)	

* Relationship with health literacy groups and categorical data, **Relationship between health literacy index and categorical data

best of our knowledge, our study is the first study that evaluates the health literacy of patients who applied to the family medicine clinic of a tertiary hospital in Turkey.

Studies on health literacy of countries reveal that there are differences between health literacy levels between countries. Low health literacy is a global public health problem. In a study conducted in the USA, it was revealed that about 80 million adults in the USA have poor health literacy (6). In the study conducted by Sørensen et al.(7), on a total of 8000 people, approximately 1000 people selected from each community, in 8 countries in Europe (Austria, Ireland, Bulgaria, Spain, Poland, Germany, Netherlands, Greece), it was revealed that health literacy differs between countries. In this study, the average general health literacy scores were found to be highest in the Netherlands with 37.06 and Ireland with 35.16, and the lowest in Bulgaria with 30.50 and Austria with 31.95. The general health literacy average score of 8 countries in the study was determined as 33.78 (7). On the other hand, Nakayama et al. (8) reported in their study that a high level of development in a country does not mean that it has a high level of health literacy. In the current study, health literacy levels were found similar to the European health literacy mean values reported in the study of Sørensen et al. (7)

The first large-scale research in Turkey was conducted by the Health and Social Service Workers Union in 2014 (3). As a questionnaire and scoring system evaluating health literacy for the Turkish society has not been established until this date, the Health Literacy Questionnaire-European Union has been translated into Turkish within the scope of this study, and validity tests have been carried out and brought to the Turkish literature. In this study, it was stated that the general health literacy levels of the participants were 64.6% inadequate or problematic and 35.4% sufficient or excellent. In a study conducted in Turkey with emergency service patients using the TSOY-32 scale in 2019, it was determined that 57.9% of the participants had inadequate health literacy levels (9). Berberoğlu et al. (10) evaluated the health literacy level of adult patients who applied to the family health center in their study. As a result of this study, 51.7% of the participants reported that their health literacy was inadequate. Similarly, Gözlü and Kaya (11) showed that 61.3% of the participants in their study at the family health center had inadequate or problematic health literacy levels. In our study, this rate was 44.3%. A plausible explanation for the divergent results from the study of Gözlü and Kaya (11) may be that our cohort was younger. Because there was a negative correlation between the health literacy index and age in both studies. Another plausible explanation may be that our study was conducted after the pandemic and there was intensive information about health during the pandemic period (12).

In the current literature, it has been observed that the level of health literacy decreases with age. In a study by Baker et al. in the United States with 2774 geriatric participants, they showed that as age increases, the level of health literacy decreases (13). Similarly, in other studies conducted with the same scale that we used in our study, a decrease in the level of health literacy was observed with age, as in our study (10,14). This may be related to the fact that young people have easier access to information and better use of technology.

There are conflicting publications in the literature regarding the relationship between health literacy level and education level. In the study of Yakar et al. in which they examined the health literacy levels of patients who applied to a university hospital outpatient clinic and the affecting factors, they reported that there was a relationship between low health literacy level and low education level (15). Ilgaz from Turkey showed that there is a relationship between health literacy and education level in a study with 320 participants (16). In her study, Arendt emphasized with her findings that those with higher education levels may not always have higher health literacy level (17). In our study, as study of Özdemir et al. showed that there is no relationship between education level and health literacy in their study (9). The explanation for not showing a relationship between education level and health literacy may be that people have benefited from resources that will improve health literacy according to their interests, according to their capacities.

An important limitation of our study was that it was single center study. Multi-center studies are needed for more generalizable results. Another limitation was that our study cohort was relatively young. The relatively young nature of our cohort is another factor limiting the generalizability of our study. Our study can be repeated with more homogeneous groups. On the other hand, our study was carried out during the pandemic period. Current study can be repeated by considering the effects of the health education on society during the pandemic period.

CONCLUSION

Low health literacy is an important public health problem. Health literacy can be considered as a priority policy issue. Legal arrangements can be made to carry out activities for health literacy. In order to increase the level of health literacy of individuals and the society, public service announcements and training programs can be prepared by acting together with other important stakeholders such as the Ministry of Health and the Ministry of Education, non-governmental organizations, academic communities and the media.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study approved by Clinical Research Ethics Committee of Ümraniye Training and Research Hospital (Date: 30.09.2021, Decision no: B.10.1.TKH.4.34.H.GP.0.01/285).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study had received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Simonds SK. Health education as social policy. Health Educ Monograph 1974; 2: 1-25.
2. Health literacy: Report of the council on scientific affairs. Ad hoc committee on health literacy for the council on scientific affairs, American Medical Association. JAMA 1999; 281: 552-7.
3. Durusu Tanrıöver M, Yıldırım HH, Demiray Ready FN, Çakır B, Akalın HE. Turkey Health Literacy Survey. Health and Social Workers Union; Ankara, 2014. Available from: http://www.sagliksen.org.tr/cdn/uploads/gallery/pdf/8dcec50aa18c21cdaf86a2b33001a409.pdf
4. Okyay P, Abacıgil F. Turkish Health Literacy scales reliability and validity study 1. Edition. Ankara 2016; 1-104
5. Şantaş G. Health Literacy Studies in Turkey: a content analysis for graduate theses. TFSD 2021; 2: 54-60.
6. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med 2011; 155: 97-107.
7. Sørensen K, Pelikan JM, Röthlin F, et al. Health literacy in Europe: Comparative results of the European Health Literacy Survey (HLS-EU). EJPH 2015; 6: 1053-8.
8. Nakayama K, Osaka W, Togari T, et al. Comprehensive health literacy in Japan is lower than in Europe: a validated Japanese-language assessment of health literacy. BMCPH 2015; 15: 505.
9. Özdemir S, Akça HŞ, Algın A, Kokulu K. Health literacy in the emergency department: a cross-sectional descriptive study. Eurasian J Emerg Med 2020; 19: 94-7.
10. Berberoğlu U, Öztürk O, İnci MB, Ekerbiçer HÇ. Evaluation of Health Literacy Status of Individuals aged 18-65 years registered in a Family Health Center. Sakarya Med J 2018; 8: 575-81.
11. GözlüK, Kaya S. Evaluation of health literacy level of patients applied to family health centers: the case of Cankaya district. Ankara Med J 2020; 20: 254-68.
12. Özdemir S, Algın A. How will the health literacy and crowded emergency room be affected after the COVID-19 pandemic? Phnx Med J 2021; 3: 50-50.
13. Baker DW, Gazmararian JA, Sudano J, Patterson M. The association between age and health literacy among elderly persons. J Gerontol B Psychol Sci Soc Sci 2000; 55: 368-74.
14. Durmaz S, Sürücü EE, Özvurmaz S. Mermer fabrikası işçilerinde sağlık okuryazarlığı, sağlık algısı düzeyleri ve ilişkili faktörlerin belirlenmesi. Med Sci 2020; 15: 81–91.
15. Yakar B, Gömleksiz M, Pirinççi E. Bir üniversite hastanesi polikliniğine başvuran hastaların sağlık okuryazarlığı düzeyleri ve etkileyen faktörler. Euras J Fam Med 2019; 8: 27-35.
16. Ilgaz A. Bir Aile Sağlığı Merkezi'ne kayıtlı bireylerde sağlık okuryazarlığı seviyesi ve ilişkili faktörler. Hacettepe Üniversitesi Hemşirelik Fakültesi Derg 2021; 151-9.
17. Arendt JN. Does education cause better health? A panel data analysis using school reform for identification. Economics of Educ Rev 2005; 24: 149-60.

Case Report

HEALTH SCIENCES
MEDICINE

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Can anti-IgE and anti-IL-5 monoclonal antibodies be protective against household transmission of SARS-CoV-2?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is the general term used for pneumonia caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Keeping the infected individuals in quarantine is very effective in preventing the spread of the disease but isolation and quarantine period increase the risk of household transmission. By December 2020, the rate of household transmission of SARS-CoV-2 has reached up to 85%. Both omalizumab and mepolizumab are used for the treatment of severe persistent asthma. In addition, omalizumab also has an indication for use in chronic urticaria. Both medications have been shown to have some antiviral effects. So, we aimed to discuss potential protective effects of these agents against household transmission of SARS-CoV-2 by reporting six different patients who remained uninfected despite PCR (Polymerase Chain Reaction) (+) SARS-CoV-2 individuals at home and were being treated with monoclonal antibodies.

Keywords: Mepolizumab, omalizumab, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is the general term used for pneumonia caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and since the first identification of SARS-CoV-2 it has caused one of the greatest pandemics of human history (1). The disease presents with complaints such as high temperature, cough, and sore throat. Infected wild animals and infected humans are the most important sources of transmission (2). Although some vaccines have come into use, there is still no definitive medical treatment for the disease, and handwashing, social distancing, use of masks, and isolation of the infected individuals comprise the most important stages in protection against transmission of the disease (3). Keeping the infected individuals in quarantine is very effective in preventing the spread of the disease but isolation and quarantine period increase the risk of household transmission (4). By December 2020, the rate of household transmission has reached up to 85% (5). Omalizumab is an anti-immunoglobulin (Ig) E and mepolizumab, however, anti-interleukin (IL)-5 antibody. Both medications are used for the treatment of severe persistent asthma in patients with suitable phenotype. In addition, omalizumab also has an indication for use in chronic urticaria. Apart from these effects, both medications have been shown to have some antiviral effects (6). In this case series, we aimed to discuss potential protective effects of these agents against household SARS-CoV-2 transmission in the light of the literature by reporting six different patients who remained uninfected despite PCR (Polymerase Chain Reaction) (+) SARS-CoV-2 individuals at home and were being treated with monoclonal antibodies for chronic urticaria or severe persistent asthma.

CASE

Patient 1: A 37-year-old female patient suffering from severe asthma for five years had been using omalizumab at a dose of 450 mg/4 weeks/subcutaneous for the last 3 years in addition to her current treatment for asthma (vilanterol/fluticasone 100/25 mcg, 1x1, inh; montelukast 10 mg, 1x1, po). During the pandemic, the patient continued omalizumab treatment. In the prick test of the patient, the patient had sensitivities to grass pollen and house dust mites. The patient was being concomitantly treated for allergic rhinitis and chronic sinusitis (Ketotifen hydrogen 2 mg, 2x1, po; fluticasone propionate 2x1, intranasal). The patient did not admit to the emergency department, was not hospitalized, or given systemic steroids due to symptoms of asthma exacerbations within the last 2 years. The Father of

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the patient whose daughter, husband, and father who was living in the same house were found to be SARS-CoV-2 PCR (+) in December 2020 died of COVID-19. Despite living together with 3 SARS-CoV-2 PCR (+) individuals, the patient had no complaint consistent with COVID-19 and was found to be SARS-CoV-2 PCR (-). Her chest x-ray showed no pathology.

Patient 2: A 35-year-old male patient suffering from severe asthma, chronic rhinosinusitis, and nasal polyps for four years had been using mepolizumab at a dose of 100 mg/4 weeks/sc for the last 10 months in addition to his current treatment for asthma (montelukast 10 mg, po, 1x1; formoterol/fluticasone 12/500 mcg 2x1, inh). During the pandemic, he continued his regular mepolizumab treatment. After mepolizumab, the patient did not admit to the emergency department, was not hospitalized, or given systemic steroids due to symptoms of asthma exacerbations. Despite the fact that his 3 children and wife were found to be SARS-CoV-2 PCR (+) in December 2020, our patient had no complaint. His chest x-ray was normal and he had a negative SARS-CoV-2 PCR test.

Patient 3: A patient who had been using omalizumab due to chronic urticaria for two years got pregnant after initiation of omalizumab treatment and his omalizumab treatment was continued during pregnancy. In addition, the patient, who was on a diet and using insulin glargine 1x24 units/ sc for gestational diabetes mellitus, were using L-thyroxine 75 mcg, po, 1x1 due to Hashimoto's thyroiditis. Although her husband was found to be SARS-CoV-2 PCR (+) at 6 months of pregnancy, the patient who continued her regular omalizumab treatment was found to be SARS-CoV-2 PCR (-) and she had no complaint consistent with COVID-19.

Patient 4: A patient followed-up with allergic asthma for eighteen years had been given 13 doses of omalizumab treatment at a dose of 300 mg/4 weeks/subcutaneous in addition to levocetirizine/montelukast 5/10 mg, 1x1, po and beclomethasone dipropionate/formoterol fumarate 100/6, 2x1, inh for treatment of asthma. Although his parents living in the same house with him were found to be SARS-CoV-2 PCR (+), he had no complaint and was found to have a negative SARS-CoV-2 PCR test.

Patient 5: A 52-year-old female patient who was being followed-up with a diagnosis of asthma for twenty years and had sensitivities to cockroaches and home dust mites was using mepolizumab treatment at a dose of 100 mg/4 weeks/ sc for 9 months in addition to her current treatment for asthma. Although the daughter and husband of the patient who continued to her regular mepolizumab treatment during the pandemic were found to be SARS-CoV-2 PCR (+), she was found to have a negative SARS-CoV-2 PCR test.

Patient 6: A 37-year-old female patient had been followed-up with a diagnosis of chronic urticaria for eight years and had received a total of 30 doses of omalizumab at a dose of 300 mg/4 weeks/ sc due to intermittent recurrences within the last 3 years. The patient who also had obesity in addition to chronic urticaria were using ketotifen 2 mg, po,1x1; montelukast sodium 10 mg, po, 1x1; and Fexofenadine 180 mg/1x1/ po. Despite the fact that her sister and mother living in the same house with her were found to be SARS-CoV-2 PCR (+), no symptoms suggesting COVID-19 were observed and the patient was found to be SARS-CoV-2 PCR (-).

Table 1. The demographic and clinical properties of the patients

	Age	G	Diagnosis	Duration of disease	Monoclonal antibody	Number of injections	SARS-CoV-2 PCR (+) family members	Other treatments	Comorbidities
Patient A	37	F	Severe asthma	5 years	Omalizumab	36	Father, Husband, Daughter	-Vilanterol/ fluticasone 100/25 mcg, 1x1, inh -Montelukast 10 mg, 1x1, po	-Allergic rhinitis -Chronic sinusitis
Patient B	35	M	Severe asthma	4 years	Mepolizumab	10	Wife, Three children	-Montelukast 10 mg, po -Formoterol/fluticasone 12/500 mcg 2x1, inh	-Chronic rhinosinusitis -Nasal polyps
Patient C	29	F	Chronic urticaria	2 years	Omalizumab	7	Husband	-Cetirizine 10 mg, 1x1, po	-Gestational diabetes mellitus -Hashimoto's thyroiditis
Patient D	23	M	Severe asthma	18 years	Omalizumab	13	Mother, Father	-Levocetirizine/ montelukast 5/10 mg, po -Beclomethasone dipropionate/ formoterol fumarate 100/6, 2x1, inh	-None
Patient E	52	F	Severe asthma	20 years	Mepolizumab	9	Daughter Husband	-Montelukast sodium 10 mg, 1x1, po -Formoterol/fluticasone 12/500 mcg 2x1, inh	
Patient F	37	F	Chronic urticaria	8 years	Omalizumab	30	Sister Mother	-Ketotifen 2 mg, 2x1, po -Montelukast sodium 10 mg, 1x1, po	-Obesity

G: gender, SARS-CoV-2 PCR: Acute respiratory syndrome coronavirus 2 Polymerase Chain Reaction

DISCUSSION

COVID-19 has become one of the greatest pandemics of human history since December 2019 when it was first defined and by January 2021, it has led to the death of more than 1.900.000 people (7). One of the most effective ways of preventing the spread of the disease is the prevention of disease transmission to healthy individuals. For this purpose, the use of masks, hand washing, social distancing, and isolation of infected individuals are essential. However, quarantine of the infected individuals increases the risk of household transmission. Therefore, the reduction of household transmission also is of vital importance for the COVID-19 pandemic. Lack of SARS-CoV-2 transmission in all of the patients with different clinical diagnoses receiving a monoclonal antibody despite the presence of SARS-CoV-2 PCR (+) individual(s) in the same house suggests that injections of monoclonal antibodies like omalizumab and mepolizumab may have a protective function against SARS-CoV-2 transmission in these patients due to their some antiviral effects.

Omalizumab is a monoclonal antibody used for the treatment of antihistamine-refractory chronic urticaria and for treatment of severe asthma in atopic individuals with sensitivity to perennial allergens (8, 9). Mepolizumab, however, is an anti-IL-5 monoclonal antibody approved to be used for the treatment of eosinophilic severe asthma (10). In addition to their currently defined effects, both treatment agents have been shown to have some antiviral effects. Although The Centers for Disease Control and Prevention (CDC) defines the patients with severe asthma as a risk group for COVID-19 infection, previous studies have revealed that the prevalence of patients with asthma among patients hospitalized due to COVID-19 is lower compared to the normal population and that prevalence of asthma is relatively lower among the patients who died of COVID-19. Despite the presence of some contrary studies (11-13), patients with asthma are therefore considered not to be at high risk for SARS-CoV-2 infection (14). As the most important reasons for this situation, reduction of expression of ACE2 (angiotensin-converting enzyme 2) on the respiratory epithelial surface by inhaled steroids used for the treatment of asthma and immunomodulatory effects of the monoclonal antibodies used for treatment have been proposed (15). Gill et al. (16) reported that omalizumab exhibits an antiviral effect by down-regulating high-affinity IgE receptors on the surface of plasmacytoid dendritic cells and by reducing viral antigen presentation by dendritic cells. In addition, omalizumab enhances the interferon-mediated antiviral effectiveness of dendritic cells. In another study, Cardet et al. (17) demonstrated that omalizumab reduces TLR (Toll-like receptor)-7 expression, inhibiting triggering of natural immunity against viral antigens. There also are studies reporting that omalizumab may lead to an increase in levels of immunoglobulins other than IgE and that this situation may be beneficial for immune reconstruction in immunodeficient patients (18). Mepolizumab, however, has been shown to influence the innate and adaptive immune systems via eosinophils (19). Eosinophils also function as antigen-presenting cells in the respiratory tract, and processing and then the presentation of viral antigens by eosinophils leads to the secretion of various eosinophil-mediated cytokines and chemokines, stimulation of CD8+ T cells, and release of nitric oxide (20-22). Furthermore, increased eosinophilic activity and eosinophil-induced cytokines may also cause lung injury. The eosinophil-reducing effect of mepolizumab in tissues and plasma may reduce pulmonary epithelial injury by reducing eosinophil-induced cytokines and chemokines. Oroojalian et al. (23) demonstrated that mepolizumab binds CD147 receptor in respiratory epithelial cells, inhibiting the influx of SARS-CoV-2 virus into the target cell. Sabogal et al. (23) however, showed that mepolizumab increases local B lymphocyte and macrophage counts but reduces neutrophil count and their activation(24)(23)(24). Again, in the same study, mepolizumab was reported to cause an increase in systemic natural killer (NK) (CD3-CD19-CD56+) count, which has an antiviral effectiveness. Furthermore, mepolizumab increases secretory IgA levels and exhibits an antiviral effect also by reducing tryptase levels in the bronchoalveolar lavage fluid. Thusly, these antiviral effects of both omalizumab and mepolizumab may be protective against SARS-CoV-2 transmission and these agents may have prevented SARS-CoV-2 transmission despite the increased risk of household transmission in patients included in our case series who were receiving monoclonal antibody treatment.

CONCLUSION

Household transmission of SARS-CoV-2 is an important route of transmission. Although it is obvious that more extensive studies are needed in order to determine routes of household transmission and to reduce and/or prevent these determining factors, it should be considered that monoclonal antibodies like omalizumab and mepolizumab can make a significant contribution to the prevention of household transmission of SARS-CoV-2 with some antiviral effect and these effects should not be neglected.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval of this study was received from KTO Karatay University Medical School Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 09/02/2021, Decision No: 2021/021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Informed Consent: All patients signed the free and informed consent form.

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Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics 2020; 52: 549-57.
2. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. Int J Infect Dis 2020; 98: 180-6.
3. Qian M, Jiang J. COVID-19 and social distancing. Z Gesundh Wiss 2020: 1-3.
4. Mizumoto K, Chowell G. Transmission potential of the novel coronavirus (COVID-19) onboard the diamond Princess Cruises Ship, 2020. Infect Dis Model 2020; 5: 264-70.
5. Madewell ZJ, Yang Y, Longini IM Jr., Halloran ME, Dean NE. Household transmission of SARS-CoV-2: a systematic review and meta-analysis. JAMA Netw Open 2020; 3: e2031756.
6. Atayık E, Aytekin GJAAI. SARS-CoV-2 in a patient with persistent asthma taking omalizumab: the first case in Turkey. Asthma Allerg Immunol 2020; 18: 23-6.
7. Worldometer. COVID-19 Corona virus pandemic 2021, January 7 [Available from: https: //www.worldometers.info/coronavirus/?zarsrc=130.
8. Fick RB, Jr. Anti-IgE as novel therapy for the treatment of asthma. Curr Opin Pulm Med 1999; 5: 76-80.
9. Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. J Allergy Clin Immunol 2016; 137: 1742-50 e4.
10. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev 2017; 9: CD010834.
11. Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med 2020; 8: 436-8.
12. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020; 146: 110-8.
13. Team CC-R. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 422-6.
14. Morais-Almeida M, Aguiar R, Martin B, et al. COVID-19, asthma, and biological therapies: What we need to know. World Allergy Organ J 2020; 13: 100126.
15. Li G, He X, Zhang L, et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. J Autoimmun 2020; 112: 102463.
16. Gill MA, Liu AH, Calatroni A, et al. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. J Allergy Clin Immunol 2018; 141: 1735-43 e9.
17. Cardet JC, Casale TB. New insights into the utility of omalizumab. J Allergy Clin Immunol 2019; 143: 923-6 e1.
18. Cildag S, Senturk T. The effect of omalizumab treatment on IgE and other immunoglobulin levels in patients with chronic spontaneous urticaria and its association with treatment response. Postepy Dermatol Alergol 2018; 35: 516-9.
19. Travers J, Rothenberg ME. Eosinophils in mucosal immune responses. Mucosal Immunol 2015; 8: 464-75.
20. Sikriwal D, Seth D, Parveen S, Malik A, Broor S, Batra JK. An insertion in loop L7 of human eosinophil-derived neurotoxin is crucial for its antiviral activity. J Cell Biochem 2012; 113: 3104-12.
21. Samarasinghe AE, Melo RC, Duan S, et al. Eosinophils promote antiviral immunity in mice infected with influenza A virus. J Immunol 2017; 198: 3214-26.
22. Handzel ZT, Busse WW, Sedgwick JB, et al. Eosinophils bind rhinovirus and activate virus-specific T cells. J Immunol. 1998; 160: 1279-84.
23. Oroojalian F, Haghbin A, Baradaran B, et al. Novel insights into the treatment of SARS-CoV-2 infection: an overview of current clinical trials. Int J Biol Macromol 2020; 165: 18-43.
24. Sabogal Pineros YS, Bal SM, van de Pol MA, et al. Anti-IL-5 in mild asthma alters rhinovirus-induced macrophage, B-cell, and neutrophil responses (MATERIAL). a placebo-controlled, double-blind study. Am J Respir Crit Care Med 2019; 199: 508-17.

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