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We are proud to publish the fifth issue of our journal for 2021 with 40 articles. In this issue, there are 38 research articles, 1 review and 1 case reports. We increase the scientific quality of our journal day by day. We have followed by a wider audience over time. Principally, 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 PubMed, SCI 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 TANOGLU, MD
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Cardiovascular risk factors in polycystic ovary syndrome; the relationship of dyslipidemia and obesity

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ABSTRACT

Aim: The abnormal endocrinological picture that occurs in polycystic ovary syndrome (PCOS) has been shown to affect many systems and can lead to a wide variety of complications. In the present study, it was aimed to evaluate the role of obesity and anti-Mullerian hormone (AMH) level in the development of PCOS and to determine potential cardiac risk factors in PCOS.

Material and Method: The present study included 62 patients diagnosed with PCOS and 45 healthy women. Demographic data and laboratory results of all women were collected from hospital automation system records and were analyzed.

Results: The mean body mass index (BMI) (p=0.041), total cholesterol (p=0.038), triglyceride (p=0.022), very low-density lipoprotein (VLDL) cholesterol (p=0.003), and AMH (p<0.001) levels were significantly higher in the patient group than in the control group. The rate of women with BMI value ≥25 kg/m² was significantly higher in the patient group than that of the control group (57.6% vs. 35.6%; p=0.026). In addition, having a BMI value of ≥25 kg/m² had a 2.47-fold (odds ratio; 1.11-5.48) higher risk for PCOS development. In the ROC analysis, a threshold value of 5.495 ng/mL for serum AMH level had a sensitivity of 74.6% and a specificity of 90.9% for the diagnosis of PCOS.

Conclusion: In our study, it was concluded that obesity plays a role in the development of PCOS, the level of AMH in PCOS patients increases significantly enough to gain a diagnostic value. In addition, it was concluded that a significant dyslipidemia develops in PCOS, and that this might be a risk for the development of cardiovascular disease in the future.

Keywords: Polycystic ovary syndrome (PCOS), anti-Mullerian hormone, body mass index, dyslipidemia, cholesterol.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a polygenic endocrine disorder characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovaries. It is seen in 6-10% of women of reproductive age (1,2). It has been reported that hereditary ovarian steroidogenesis and follicular development play a role in the emergence of PCOS (1).

It has been reported that rapid gonadotropin-releasing hormone (GnRH) stimulation, over-release of luteinizing hormone (LH) and insufficient release of follicle-stimulating hormone (FSH) in PCOS lead to excessive androgen production in ovaries and cause ovulatory dysfunction (1,3). In this clinical picture, it has also been shown that insulin resistance occurs, and this leads to compensatory hyperinsulinemia, resulting in increased excess androgen release from the ovaries and adrenaline. With increased androgen production, conditions such as hirsutism, menstrual abnormalities occur (1,4).

In PCOS, 12 or more cysts with diameters of 2-9 mm are formed in one or both of the ovaries. In addition, the menstrual cycle continues at intervals of less than 21 days or longer than 35 days. In addition to these clinical pictures, hirsutism in PCOS has been reported to cause psychological abnormalities such as depression and anxiety (1,5,6).

It has been shown that the abnormal endocrinological manifestations in PCOS affect many systems and can lead to a wide variety of complications (4,5). It has been reported that women with PCOS have an increased risk for infertility, endometrial hyperplasia, cancer, abnormal glucose metabolism, metabolic syndrome, dyslipidemia, obstructive sleep apnea, depression and anxiety (1). It has been shown that increased anti-Mullerian hormone in PCOS may be associated with dyslipidemia and cardiovascular disorders (1,4).

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In the present study, it was aimed to evaluate the role of obesity and AMH level in the development of PCOS and to determine potential cardiac risk factors in PCOS.

MATERIAL AND METHOD

The study was approved by Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital Clinical Research Ethics Committee (Date: 21.08.2015, Decision No: 138). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 62 patients diagnosed with PCOS and 45 healthy women who admitted to the Gynecology and Obstetrics clinics of our tertiary hospital. This study was planned retrospectively. Demographic data and laboratory results of all women were collected from hospital automation system records and were analyzed. Informed consent was obtained from all participants. PCOS was diagnosed using Rotterdam criteria (10). According to the Rotterdam criteria, a clinical diagnosis of PCOS requires that a patient present with two of the following symptoms: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. In addition, the presence of hirsutism, one of the hyperandrogenism findings, was evaluated using the Ferriman-Gallwey scoring system (11). Physical and gynecological examinations, pelvic ultrasounds and peripheral venous blood sampling were performed on the 2nd or 3rd day of a participant's menstrual cycles. All women were examined and pelvic ultrasound scans were performed by the same gynecologist using a 7.0 MHz vaginal transducer (Voluson 730, GE Healthcare, USA) (6,7).

Patients who received medications for some diseases such as Cushing syndrome, congenital adrenal hyperplasia, pregnancy, androgen-secreting tumors, oral contraceptives, antilipidemic and/or antihypertensive drugs, steroids, diabetic drugs, anticoagulants or antiplatelet drugs were excluded from the study.

After one night fasting, blood samples of the patients were taken from the antecubital veins. For serum, biochemical and hormonal evaluation; complete blood counts were measured using fluorescent flow cytometry or electrical impedance method. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), thyroid-stimulating hormone (TSH), antimullient hormone and total testosterone were determined using commercially available enzyme-dependent immunosorbent assay (ELISA) kits (eBioscience). Glucose, insulin, total cholesterol, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol levels were measured with AutoAnalyzer.

Statistical Analysis

All statistical analyzes in the study were done using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data are given as numbers and percentages. In terms of categorical variables, comparisons between groups were made with Pearson's Chi Square test and Fisher's exact test. Kolmogorov-Smirnov Test was used to confirm whether the continuous variables were suitable for normal distribution. The differences between the groups in terms of continuous variables were analyzed using Student's t Test, and the comparison of mean values between multiple groups by variance analysis. The capacity of the AMH serum level to predict PCOS presence was analyzed using receiver operating characteristic (ROC) curve analysis. Risk coefficient of categorical variables was evaluated by logistic regression analysis and given as "odds ratio". The results were evaluated within the 95% confidence interval, and $p<0.05$ values were considered significant. Bonferroni correction was made where appropriate.

RESULTS

The mean age was 27.0±3.2 years in the patient group, and was 27.9±4.0 years in the control group. The mean body mass index (BMI) ($p=0.041$), total cholesterol ($p=0.038$), triglyceride ($p=0.022$), and very low-density lipoprotein (VLDL) cholesterol ($p=0.003$) levels were significantly higher in the patient group than that in the control group. AMH (12.0 vs. 3.0 ng/mL; $p<0.001$), total testosterone ($p<0.001$) and free testosterone ($p<0.001$) levels were significantly higher in the patient group than that the control group, and FSH was significantly lower ($p<0.001$). There was no significant difference between groups in terms of hemoglobin A1c (HbA1c) and insulin levels ($p>0.05$ for both) (**Table 1**).

Having a BMI value of ≥25 kg/m² had a 2.47-fold (odds ratio; 1.11-5.48) higher risk for PCOS development. The rate of women with BMI value ≥25 kg/m² was significantly higher in the patient group than that of the control group (57.6% vs. 35.6%; $p=0.026$). In addition, having a BMI value of ≥25 kg/m² had a 2.47-fold (odds ratio; 1.11-5.48) higher risk for PCOS development.

BMI groups were similar in terms of the mean cholesterol, triglyceride, glucose and HbA1c levels ($p>0.05$ for each) (**Table 2**).

In the ROC analysis, a threshold value of 5.495 ng/mL for serum AMH level had a sensitivity of 74.6% and a specificity of 90.9% for diagnosis of PCOS (AUC: 0.883; $p<0.001$; LB: 0.819; UB: 0.947; CI 95%) (**Figure 1**) .

Table 1. Comparison between polycystic ovarian syndrome patients and the control group in terms of the mean age, body mass index, cholesterol and hormone levels.

	PCOS (n=62)		Control (n=45)		p
	Mean	SD	Mean	SD	
Age (Years)	27.0	3.2	27.9	4.0	0.236
BMI (Kg/m²)	26.7	4.8	24.7	4.8	0.041
Ferriman Gallwey score	15.4	8.7	2.3	1.6	<0.001
Total Cholesterol (mg/dL)	180.4	35.8	167.5	23.6	0.038
Triglycerides (mg/dL)	112.8	70.5	86.4	33.7	0.022
LDL Cholesterol (mg/dL)	115.3	31.5	109.6	27.9	0.332
HDL Cholesterol (mg/dL)	46.5	10.7	49.3	9.2	0.159
VLDL Cholesterol (mg/dL)	22.3	13.6	15.8	4.9	0.003
Apolipoprotein A Subgroups (mg/dL)	153.5	23.4	155.4	15.0	0.636
Glucose (mg/dL)	90.9	11.7	92.5	7.9	0.425
Hba1c (mmol/L)	5.4	0.4	5.5	0.3	0.468
Insulin (mIU/L)	11.9	7.6	9.6	6.1	0.089
Anti-Müllerian Hormon (ng/mL))	12.0	8.0	3.0	2.8	<0.001
1,4-Delta Androstenedion (ng/mL)	3.9	1.3	2.4	1.0	<0.001
Dehydrotestosterone (ng/dL)	346.6	113.6	385.2	375.5	0.447
Total Testosterone (ng/dL)	0.5	0.2	0.3	0.1	<0.001
Free Testosteron (ng/dL)	2.6	1.0	1.8	0.9	<0.001
Progesterone (ng/dL)	1.1	2.3	1.9	3.8	0.164
17-OH Progesterone (ng/dL)	1.9	1.8	1.2	0.9	0.016
Dehydroepiandrosterone Sulfate (µg/dL)	287.3	110.9	256.4	114.4	0.164
FSH (IU/mL)	4.6	1.2	6.0	2.0	<0.001
LH (IU/L)	6.0	2.8	6.7	4.7	0.679
Prolactin (ng/dL)	16.3	12.7	18.6	14.5	0.398
Estradiol (pg/dL)	70.8	58.7	58.2	36.0	0.205
TSH (mIU/L)	1.7	0.8	1.9	1.1	0.169
T3 (ng/dL)	2.9	0.4	10.5	50.5	0.243
T4 (ng/dL)	1.0	0.1	1.0	0.2	0.882

PCOS: Polycystic ovary syndrome, SS: Standard deviation, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone. T3: Triiodothyronine T4: Thyroxine

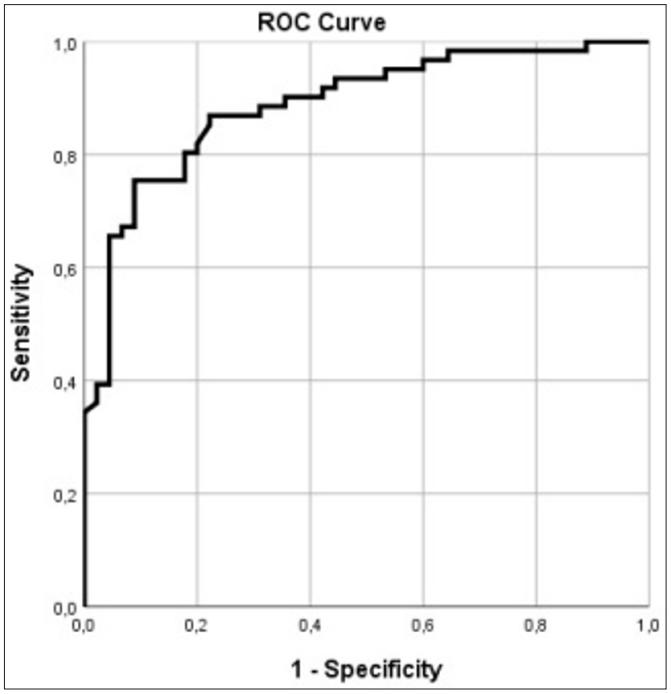

Figure 1. In the ROC analysis, a threshold value of 5.495 ng/mL for serum AMH level had a sensitivity of 74.6% and a specificity of 90.9% for the diagnosis of PCOS (AUC: 0.883; p<0.001; LB: 0.819; UB: 0.947; CI 95%).

Table 2. Mean values according to body mass index (BMI) in patient group and BMI distribution according to patient and control groups.

	BMI ≥25 (kg/m²) (n=50)		BMI<25 (kg/m²) (n=57)		p
	Mean	SD	Mean	SD	
Cholesterol (mg/dL)	181.2	37.7	180.4	35.7	0.931
Triglyceride (mg/dL)	127.7	79.4	98.4	55.3	0.119
Glucose (mg/dL)	91.1	14.4	91.0	7.7	0.973
HbA1c (mmol/L)	5.4	0.2	5.4	0.6	0.791
	n	%	n	%	
PCOS	34	57.6	25	42.4	0.022
Control	16	35.6	29	64.4	

BMI: Body mass index, SS: Standard deviation, PCOS: Polycystic ovary syndrome. HbA1c:glycosylated hemoglobin

DISCUSSION

Polycystic ovarian syndrome is an endocrinological disease that occurs in women of reproductive age due to many factors. The resulting endocrine abnormalities affect many systems in women and cause various complications. Disorders in women with PCOS significantly impair their quality of life (1,9,10). In our study, clinical features of women with PCOS were examined, and especially obesity and dyslipidemia rates were found significantly higher.

It has been stated that anti-Mullerian hormone is released from granulosa cells in small antral and pre-antral follicles and plays a role in early follicular development (11,12). It has been suggested that AMH can be used as a hormonal marker to determine the number of follicles in the ovary (13,14). Accordingly, it has been stated that AMH serum levels can reflect ovarian reserve indirectly and remain stable from cycle to cycle (11,14). It has been reported that the level of AMH in PCOS patients is significantly higher than that of healthy individuals, and this condition may be related to androgen (11,12,15). Karakas et al. (16) reported in their meta-analysis that AMH was a marker that can be used in the diagnosis, in predicting the prognosis and in predicting the response to infetrility therapy in the PCOS cases.

The total number of ovarian follicles increases in PCOS. This is especially true for antral follicles that produce large amounts of AMH (17,18). Several studies have shown that serum AMH levels above 5 ng/ml (35.7 pmol/L) can be used for the diagnosis of PCOS (19,20). Questions have been raised as the use of AMH in adolescent patients that they may have PCO morphology without the syndrome (21). However, the mean AMH concentration in adolescent girls has been shown to be about 3 ng/ml, regardless of ethnic origin (22). Therefore, serum AMH is still a valuable tool for diagnosing PCOS during adolescence. An advantage of AMH measurement is that it can be performed when transvaginal ultrasound is not available. It provides quantitation of cysts, and higher AMH concentrations may indicate more severe disease (23). The highest levels of AMH are seen when all three components of PCOS (hyperandrogenemia, anovulation and PCO) are present. Hyperandrogenism has the weakest association with AMH (19). Obesity may cause a relative decrease in AMH in PCOS patients (24). During ovulatory menstrual cycles, AMH levels are approximately 8% lower during the luteal phase compared to the follicular phase (25). However, this is not an important factor for the diagnosis of PCOS because most patients have anovulation. Combined contraceptives suppress AMH levels by about 30% to 50% over time, regardless of the route of administration (26,27). GnRH agonist leuprid administration also suppresses AMH (28). Wissing et al. (29) reported that AMH, along with BMI and androgen level, could be a reliable marker for PCOS diagnosis. All three ELISAs detecting different parts of the AMH molecule detected significantly higher levels in women with PCOS compared to control women. The relative distribution of AMH isoforms did not differ between women with PCOS and control women. AMH isoforms alone and in combination with key features predicted PCOS with close to 100% area under the receiver operating characteristic curve. It is noticeable that based on circulatory androgens, BMI, and AMH measurements, the ROC area reached 97% without measurement of AFC (15). Fleming et al. (30) found that serum AMH levels were significantly higher in PCOS patients with insulin resistance in their study conducted using HOMA-R for detection of insulin. De Kat et al. (31) found a significant relationship between age-specific AMH levels and total cholesterol levels. They also reported that high AMH levels significantly increased the risk of cardiovascular disease, which was independent of cholesterol level (31). In our study, there was no significant relationship between AMH levels and cholesterol and triglyceride levels in PCOS patients. These findings show that AMH levels have various endocrine effects, but it is not clear yet whether there is a relationship between insulin and cholesterol levels.

It has been reported that PCOS is associated with obesity (32). Lim et al. (33) determined a significant relationship between high BMI and PCOS development in their meta-analysis, and they found that high BMI values caused a 3.35-fold higher risk for PCOS development than normal BMI values. In our study, mean BMI was significantly higher in the PCOS group compared to the controls. In the risk analysis, it was determined that having BMI value of over 25 kg/m² causes 2.47-fold higher risk for PCOS development. These findings show that PCOS patients are more obese than healthy women, and obesity significantly increases the risk of PCOS development.

Neuroendocrine abnormalities may play an important role in the pathophysiology of PCOS, that they increase LH levels and decrease FSH levels by increasing GnRH (32). Wissing et al (29). found that the mean FSH level was significantly lower and the LH level was significantly higher in the PCOS group. In our study, no significant difference was found between the groups in terms of the mean LH levels. However, the mean FSH level was significantly lower in the PCOS group than the controls. These findings confirm a marked decrease in FSH levels in PCOS patients.

It has been reported that PCOS increases the risk of cardiovascular disease, and the risk increases further with age and with obesity progress (7). PCOS has been reported to be similarly associated with dyslipidemia (32). In addition, obesity has been shown to be associated with dyslipidemia in PCOS patients (33,34). It has been determined that 70% of women with PCOS can develop dyslipidemia (8). However, there is not sufficient evidence about the relationship between cardiovascular disease and PCOS in the long term yet (7). It was reported that the most frequent dyslipidemia picture that PCOS affects is triglyceridemia (8). Wissing et al. (29) found no significant difference between PCOS and control groups in terms of total cholesterol, LDL cholesterol and triglyceride levels. In our study, mean total cholesterol, triglyceride and VLDL cholesterol levels

were significantly higher in the PCOS group compared to the controls. These findings indicate that dyslipidemia develops in PCOS patients, which may cause an increased risk for cardiovascular diseases in the future.

The metabolic difficulties that occur in PCOS are related to insulin resistance and diabetes (7,32). In particular, the relationship between PCOS and obesity has been reported to pose an increased risk for insulin resistance and diabetes (7,8). In the present study, no significant difference was found between the groups in terms of HbA1c, glucose and insulin levels. This might be due to low number of the patients in our study. The present study had some limitations such as retrospective design and small sample size.

CONCLUSION

In the present study, it was concluded that obesity plays a role in the development of PCOS, that the level of AMH in PCOS patients increases significantly enough to gain a diagnostic value, that a significant dyslipidemia develops in PCOS, and that this might be a risk for the development of cardiovascular disease in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Zeynep Kamil Gynecology and Pediatrics Training and Research Hospital Clinical Research Ethics Committee (Date: 21.08.2015, Decision No: 138).

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. McCartney CR, Marshall JC. Clinical Practice. Polycystic Ovary Syndrome N Engl J Med 2016; 375: 54-4.
2. Meier RK. Polycystic Ovary Syndrome. Nurs Clin North Am 2018; 53: 407-20.
3. Nandi A, Chen Z, Patel R, Poretsky L. Polycystic ovary syndrome Endocrinol Metab Clin North Am 2014; 43: 123-47.
4. Rothenberg SS, Beverley R, Barnard E, Baradaran-Shoraka M, Sanfilippo JS. Polycystic ovary syndrome in adolescents. Best Pract Res Clin Obstet Gynaecol 2018; 48: 103-14.
5. Li L, Feng Q, Ye M, He Y, Yao A, Shi K. Metabolic effect of obesity on polycystic ovary syndrome in adolescents: a meta-analysis. J Obstet Gynaecol 2017; 37: 1036-47.
6. Bani Mohammad M, Majdi Seghinsara A. Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. Asian Pac J Cancer Prev 2017; 18: 17-21.
7. Pigny P, Jonard S, Robert Y, Dewailly D. Serum anti-Mullerian hormone as a surrogate for antral follicle count for definition of the polycystic ovary syndrome. J Clin Endocrinol Metab 2006; 91: 941-5.
8. Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril 2011; 95: 1073-9.
9. Barthelmess EK, Naz RK. Polycystic ovary syndrome: current status and future perspective. Front Biosci (Elite Ed) 2014; 6: 104-19.
10. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 2011; 7: 219-231.
11. Łebkowska A, Kowalska I. Anti-Müllerian hormone and polycystic ovary syndrome. Endokrynol Pol 2017; 68: 74-8.
12. Bani Mohammad M, Majdi Seghinsara A. Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. Asian Pac J Cancer Prev 2017; 18: 17-21.
13. Pigny P, Jonard S, Robert Y, Dewailly D. Serum anti-Mullerian hormone as a surrogate for antral follicle count for definition of the polycystic ovary syndrome. J Clin Endocrinol Metab 2006; 91: 941-5.
14. Feldman RA, O'Neill K, Butts SF, Dokras A. Antimüllerian hormone levels and cardiometabolic risk in young women with polycystic ovary syndrome. Fertil Steril 2017; 107: 276-81.
15. Tata B, Mimouni NEH, Barbotin AL, et al. Elevated prenatal anti-Müllerian hormone reprograms the fetus and induces polycystic ovary syndrome in adulthood. Nat Med 2018; 24: 834-6.
16. Karakas SE. New biomarkers for diagnosis and management of polycystic ovary syndrome. Clin Chim Acta 2017; 471: 248-53.
17. Bhide P, Dilgil M, Gudi A, Shah A, Akwaa C, Homburg R. Each small antral follicle in ovaries of women with polycystic ovary syndrome produces more antiMullerian hormone than its counterpart in a normal ovary: an observational cross-sectional study. Fertil Steril 2015; 103: 537–41.
18. Homburg R, Ray A, Bhide P, et al. The relationship of serum anti-Mullerian hormone with polycystic ovarian morphology and polycystic ovary syndrome: a prospective cohort study. Hum Reprod 2013: 28: 1077–83.
19. Sahmay S, Atakul N, Aydogan B, Aydin Y, Imamoglu M, Seyisoglu H. Elevated serum levels of anti-Mullerian hormone can be introduced as a new diagnostic marker for polycystic ovary syndrome. Acta Obstet Gynecol Scand 2013; 92: 1369–74.
20. Saikumar P, Selvi VK, Prabhu K, Venkatesh P, Krishna P. Anti Mullerian hormone: a potential marker for recruited non growing follicle of ovarian pool in women with polycystic ovarian syndrome. J Clin Diagn Res 2013; 7: 1866–9.
21. Agapova SE, Cameo T, Sopher AB, Oberfield SE. Diagnosis and challenges of polycystic ovary syndrome in adolescence. Semin Reprod Med 2014; 32: 194–201.
22. Elchuri SV, Patterson BC, Brown MR, Buchanan I, Mertens AC, Meacham LR. Anti-Mullerian hormone levels in American girls by age and race/ethnicity. J Pediatr Endocrinol Metab 2015; 28; 189–93.
23. Koninger A, Koch L, Edimiris P, et al. Anti-Mullerian hormone: an indicator for the severity of polycystic ovarian syndrome. Arch Gynecol Obstet 2014; 290: 1023–30.
24. Piouka A, Farmakiotis D, Katsikis I, Macut D, Gerou S, Panidis D. Anti-Mullerian hormone levels reflect severity of PCOS but are negatively influenced by obesity: relationship with increased luteinizing hormone levels. Am J Physiol Endocrinol Metab 2009; 296: 238–43.

25. Schiffner J, Roos J, Broomhead D, et al. Relationship between anti-Müllerian hormone and antral follicle count across the menstrual cycle using the Beckman Coulter Access assay in comparison with Gen II manual assay. Clin Chem Lab Med 2017; 55: 1025-33.
26. Bentzen JG, Forman JL. Pinborg A, et al. Ovarian reserve parameters: a comparison between users and non-users of hormonal contraception. Reprod BioMed Online 2012; 25: 612–9.
27. Kallio S, Puurunen J, Ruokonen A, Vaskivuo T, Piltonen T, Tapanainen JS. AntiMullerian hormone levels decrease in women using combined contraception independently of administration route. Fertil Steril 2013; 99: 1305–10.
28. Su HI, Maas K, Sluss PM, Chang RJ, Hall JE, Joffe H. The impact of depot GnRH agonist on AMH levels in healthy reproductive-aged women. J Clin Endocrinol Metab 2013; 98: 1961–6.
29. Wissing ML, Mikkelsen AL, Kumar A, et al. Associations of different molecular forms of antimüllerian hormone and biomarkers of polycystic ovary syndrome and normal women. Fertil Steril 2019; 112: 149-55.
30. Fleming R, Harborne L, MacLaughlin DT, et al. Metformin reduces serum mullerian-inhibiting substance levels in women with polycystic ovary syndrome after protracted treatment. Fertil Steril 2005; 83: 130-6.
31. De Kat AC, Verschuren WM, Eijkemans MJ, Broekmans FJ, van der Schouw YT. Anti-Müllerian hormone trajectories are associated with cardiovascular disease in women: results from the Doetinchem Cohort Study. Circulation 2017; 135: 556-65.
32. Bozdag G, Yildiz BO. Interventions for the metabolic dysfunction in polycystic ovary syndrome. Steroids 2013; 78: 777-81.
33. Glueck CJ, Goldenberg N. Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics. Metabolism 2019; 92: 108-20.
34. Caldwell AS, Middleton LJ, Jimenez M, et al. Characterization of reproductive, metabolic, and endocrine features of polycystic ovary syndrome in female hyperandrogenic mouse models. Endocrinology 2014; 155: 3146-59.

Original Article

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Comparison of the timed limb coordination according to comorbidity level in community dwelling older adults

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ABSTRACT

Aim: The prevalence of chronic disease increases with aging. It is very important to examine the effects of comorbidity in older adults. The aim of this study is to compare the timed limb coordination according to comorbidity level in community dwelling older adults.

Material and Method: Ninety six older adult were included. The socio-demographic data (age, height, weight, educational level, etc) recorded. Modified Charlson comorbidity (mCCI) index assessed comorbidity levels of older adults. The older adults performed timed limb coordination tests for upper and lower limb. The participants were divided into two groups in terms of their comorbidity (low comorbidity; mCCI<3, high comorbidity; mCCI ≥3).

Result: Forty-eight participants (26 females, 22 males, mean age 69.40±2.64) had low comorbidity level, the other 48 individuals (32 females, 16 males, mean age 72.26±6.04) had high comorbidity level. The age, gender, body mass index, cognitive status and education status were similar between groups (p>0.05). The participants with low comorbidity were found to have better timed limb coordination (p<0.001).

Conclusion: We determined that the presence of chronic disease affects timed limb coordination in Turkish older adults. It may be important to investigate the effects of comorbidity, balance and coordination exercise programs were included physiotherapy programs in reducing the negative features of comorbidity in future studies.

Keywords: Ageing, comorbidity, coordination impairment

INTRODUCTION

With the increase in life expectancy, the number of older adult living with more than one chronic medical condition is also increasing worldwide. Widely defined as the co-emergence of two or more chronic medical conditions in an individual, multimorbidity affects up to one-fourth of older adult who need primary care (1,2). Comorbidity, which is defined as three or more chronic conditions affecting the system of the body, requires a higher rate of using health services (3). A study has revealed that people with more than one chronic disease correspond to a rate above 60%, and this rate reaches 80% in individuals aged above 85 across the world (4). In parallel with the increase in the geriatric population, the incidence and prevalence of chronic diseases, which lead to mortality, are also increasing (4). Chronic diseases result in health outcomes such as physical dysfunctions, an increase in dependency and healthcare costs, a decrease in health-related life quality, and early death (5). Furthermore, progressive physical changes such as cognitive disorders and a decrease in muscular strength, proprioception, reaction time, and joint range of motion occur as the incidence of chronic diseases increases (5). Consequently, it is extremely important to know the effects of chronic diseases on health and to plan the appropriate and timely interventions to reduce the negative effects of comorbidity at later ages.

Limb coordination is a generalized form of coordination. These coordination involves peripheral (muscular, sensory) and central (neural coupling, information processing) processes. Limb coordination refers to the ability to move two parts of the body synchronously in certain patterns of repetitive kinematic movement without the need to adapt them to the environment. A decrease in the ability to coordinate the two limb

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segments may reflect a central dysfunction that generalizes to other forms of coordination and functional task performance (6,7). With ageing, limb coordination is also affected (7). Upper limb coordination plays a critical role in daily living activities. For example for self-care, including feeding, dressing. Lower limb coordination is also important and contribute to gross motor skills such as crawling, walking, balance recovery (8). Hollman et al. (9), controlling for the effects of sex, age and height, reported that timed lower limb coordination (heel-on-shin performance) were associated with walking speed. Therefore, timed limb coordination is very important in daily living activities and continuing mobility and balance activities.

Limb coordination is assessed by tests that examine a person's ability to perform alternative or reciprocal movements and movement synergies accurately and quickly (10). In the literature, limb coordination test batteries have usually been used to evaluate patients with specific pathologies. Furthermore, it has been determined that with a decrease timed limb coordination with ageing and changes in both upper and lower limb coordination performance are common in older adult (9). In the literature, it is stated that the presence of chronic disease affects mobility and gait speed in older adult (11). However, there are no studies investigating timed limb coordination by considering comorbidity level in community dwelling older adults. Therefore, the aim of this study is to compare the timed limb coordination according to comorbidity level in community dwelling older adults.

MATERIAL AND METHOD

Participants

This study was conducted on a total of 96 older adult aged above 65 years. Ethical permission for the study was obtained from Kırıkkale University Non-invasive Research Ethics Committee (Date: 26.08.2020, Decision No: 2020.07.03). Written informed consent was obtained from all individuals participating in the study.

Our study included individuals who were aged 65 years and above, could read and understand Turkish, had the Mini-Mental State Examination (MMSE) score of 24 and above, could walk 10 meters independently or with an assistive device, who voluntarily agreed to participate in our study and signed the consent form. Individuals who were still receiving inpatient treatment, had difficulty understanding the desired tasks cognitively, with missing or lost data, using drugs that could affect balance, had severe musculoskeletal system or neurological disorders, and those who needed someone else's help during ambulation were excluded from the study.

The socio-demographic data (age, height, weight, educational level, etc) all the individuals who participated in the study recorded. The Mini Mental State Examination (MMSE) was used to determine general cognitive status of older adults. Afterward, the modified Charlson comorbidity index, timed limb coordination tests were applied. The participants were divided into two groups in terms of their comorbidity (low comorbidity; mCCI<3, high comorbidity; mCCI ≥3) (12).

The sample calculation was made according to the data we obtained from the pilot study. In the power analysis using the G*Power version 3.1.9.6 it was predicted that at least 46 people were taken for both groups with an effect size of 0.60 and power 80% (alpha; 0.05, two tailed).

Instruments

Mini-Mental State Examination (MMSE): The Mini-Mental State Examination (MMSE) was used in our study for cognitive state evaluation. The MMSE was used by Folstein et al. (13) in 1975 for the first time. The scale was produced as a cognitive assessment tool that can be applied in a short time to examine older adult. The highest score that can be obtained from this test is 30, and there is no time limitation. In the scoring, 24-30 points are accepted as normal, 18-23 points are compatible with mild dementia, 10-17 points are compatible with dementia, 10 points and below are compatible with severe dementia. Its Turkish validity study was performed by Güngen et al. (14).

Modified Charlson Comorbidity Index (mCCI) ; The purpose of this index, which was created by Charlson et al. (15) in 1987, is to develop a prospectively applicable method to estimate the risk of death from the comorbid disease. In the index, numerical values between 0-37 are obtained by giving scores ranging from 1 to 6 to 19 diseases that are the main cause of morbidity. The index was revised by Beddhu et al. (16), the age factor was also added to the scoring (additional 1 point to every 10 years after the age of 40), and it was called the modified Charlson comorbidity index. Comorbidity level classification is low level (score <3), high level (score ≥3) comorbidity.

Timed Limb Coordination Tests

For the upper limb; Finger-to-nose test: According to the methods explained by Lanzino et al. (10), the participant alternately touched the fingertip of a person who made an evaluation and his own nose as quickly and accurately as possible, held approximately at eye level within the reach of the participant's arm. After an application trial, the time required to complete 5 repetitions of the finger-to-nose test was recorded in seconds. Since timed limb coordination tests did not differ between dominant and non-dominant limbs, the test was performed only on the dominant limb.

Pronation-supination test: With the elbows in the flexion position at 90° and held close to the body, the participant

completed the supination and pronation movement alternately in the dominant limb. After an application trial, the time required to complete 5 repetitions of the pronation-supination test was recorded in seconds (10).

For the lower limb; Knee-to-heel test: The participant placed the heel of one foot on the ankle of the opposite side while in the supine position. It was shifted alternatively from the ankle to the knee, from the knee to the ankle. After an application trial, the time required to complete 5 repetitions of the knee-to-heel test was recorded in seconds (10).

Statistical Analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc, Chicago, IL, USA). Kolmogorov-Smirnov/Shapiro-Wilk's were used to show that the variables whether or not normally distributed. Numerical variables were presented as mean and standard deviation (SD) or median (minimum-maximum) and categorical variables as frequency percentage (%) in descriptive analysis. The gender and education level distribution of the groups were analyzed using the Chi-square test. Non-parametric variables between groups were compared using the Mann-Whitney U test. Statistical significance was accepted as $p<0.05$.

RESULTS

Fifty-eight (60.4%) of the 96 older adult who participated in our study were female, and 38 (39.6%) were male. The mean age is 73.83±6.16 years. The general descriptive characteristics of the older adult who participated in the study are presented in **Table 1** according to their comorbidity status. Both groups were found to be statistically similar in terms of sex distribution, age, height, weight, BMI, and MMSE ($p>0.05$) (**Table 1**). While 48 participants (26 females, 22 males) had low comorbidity, the other 48 individuals (32 females, 16 males) had high comorbidity.

Table 1. Characteristics of the participants

	Low comorbidity (Mean±SD) (n=48)	High comorbidity (Mean±SD) (n=48)	p value
Age (years)	69.40±2.64	72.266.04	0.624
Gender n (%)			
Female	26 (54.1)	32 (66.6)	0.834
Male	22 (45.8)	16 33.3)	0.743
Height (cm)	162.62±7.42	161.34±8.12	0.622
Weight (kg)	75.10±11.90	72.34±10.43	0.746
BMI (kg/m^2)	28.83±4.47	28.37±5.54	0.808
Education status (n) (%)			0.754
Secondary school	22 (45.8)	26 (54.1)	
High school	16 (33.3)	14 (29.1)	
Collage/university	10 (20.8)	8 (16.6)	
MMSE (score)	27.10±1,80	26.38±2.70	0.832
mCCI (min-max)	1 (1-3)	6 (4-10)	0.001*

SD; Standard Deviation, cm; centimeter, kg; kilogram, %: percentage n: participants BMI; Body Mass Index, MMSE; Mini Mental State Examination, mCCI; Modified Charlson Comorbidity Index, *p<0.05

The supination-pronation test, finger to nose test, knee to heel test results were found to be significantly different between groups ($p<0.001$). These values were better in older adults with low comorbidity (**Table 2**).

Table 2. Timed limb coordination of participants according to comorbidity level

	mCCI<3 (mean±SD)	mCCI≥3 (mean±SD)	p value
Supination-Pronation Test	5.78±1.62	9.83±4.62	<0.001*
Finger-to-Nose	7.70±2.02	10.91±4.43	<0.001*
Knee-to-Heel	7.87±2.17	11.87±5.38	<0.001*

*p<0.05, SD; Standard Deviation, mCCI; Modified Charlson Comorbidity Index,

DISCUSSION

This study made a significant contribution to the literature in terms of revealing the effect comorbidity level on timed limb coordination in older adults. In light of these results, we determined that the presence of high chronic disease level affects coordination in older adult. We think that this may cause disability by affecting the quality of life of older adult and their independence in daily living activities. These results showed that high comorbidity level effect the timed limb coordination required for functional independence in older adult.

Limb coordination varies depending on peripheral factors and central processes. Peripheral factors such as asymmetries in strength, power, range of motion and the timing of upper and lower extremity movements are affected during the aging process (17). James et al. (18) was reported that upper extremity coordination is a risk factor for subsequent mobility limitations may be due to central neurological function that affects the upper as well as lower extremities. In the literature, studies has shown that proper performance of ryhtmic cooordination depends on the ability of the central nervous system to inhibit the default in neuromotor coupling limbs (19). Aging process is associated with decreased inhibitation of neuromotor coupling (20). Decline in these central process may give rise to impaired limb or other forms of coordination that in turn leads to the development of mobility limitations in older adults. In the neural organization of motor behavior, the coordination of body segmentsis very important and plays a central role (21). Studies showed that impairments in limb coordination were associated with mobility limitations is consistent with theoretical views of coordination as important to the production of effective movement patterns (22). James et al. (23) reported that lower extremity coordination has a meaningful association with mobility limitation. Their finding that even upper body coordination impairment is associated with lower body limitations.

In the literature, there are no studies examining timed limb coordination according to comorbidity level in older adult. Our study contributes significantly to the literature in this respect. Normally coordinated limb movements are characterized by rhythmic muscle contractions and relaxations that support easy reversal between opposing muscle groups and proximal stability that allows distal mobility. These features of coordinated limb movements are also important features of gait (9). In a study examining coordinated limb movements and gait speed in healthy older adult, timed limb coordination was found to be associated with gait speed (9). Hollman et al. (9) reported that the basis for the relationship between timed limb coordination and walking speed may be associated with underlying neural mechanisms that affect the speed and limb coordination. They stated that the speed of performance, in part, by internal neural properties shared by the neural generators of alternating upper limb movements and neural generators of gait. Their findings supports their hypothesis that both walking speed and timed limb coordination performance decrease with age.

There are many studies in the literature showing that comorbidity and walking speed are affected. Gait speed assessment represents a valuable tool in the clinical evaluation of frailty, and there is an association between lower gait speed and reduced strength, power, coordination, and balance (24). Studies in the literature have emphasized that comorbidities adversely affect gait speed, and according to the NICE multimorbidity guidance, gait speed should definitely be evaluated in older adult with chronic disease who require primary care (25). Ortiz et al. (26) revealed a relationship between multimorbidity and gait speed in older adult without functional deficit and stated that the gait speed coefficient decreased up to 0.2 m/sec in older adult with 3 and more chronic diseases. Since we thought that timed limb coordination, which is associated with gait speed, might also be affected by comorbidity, we examined the effect of comorbidity level on timed limb coordination in our study. As a result, we determined that comorbidity level affects limb coordination. We think that affecting limb coordination in individuals with chronic diseases will lead to balance disorders and increase the risk of falls and cause falls. Increasing chronic diseases adversely affect timed limb coordination in individuals, increase the risk of falls, and make individuals more dependent. Therefore, older adult with chronic diseases should be definitely evaluated in detail in terms of falling risks and should be included in strength, balance and coordination exercise training programs.

When the demographic data of the individuals participating in our study were examined, there was no difference between the groups in terms of age, sex, BMI, and MMSE. Lanzino et al. (10) reported that timed limb performance times were slower in the 80+ group than the 60-69 group all upper extremity limb coordination tests and slower in the 80+ group than the 70-79 group in the finger to nose and pronation-supination tests. Therefore, individuals of similar age groups were included in our study. However, when they examine the effect of sex on timed limb performance, they specified that men performed faster than women during pronaton-supination and heel-on-shin tests. Sex distribution between groups was similar in our study. At the same time they reported that height negatively correlated with performance time for all upper and lower extremity timed limb tests. However, it has been determined that BMI has no effect on test performance times. Therefore, in our study, older adult with similar height were included in the groups since height might affect our results. Moreover, according to the results obtained from the study, timed limb coordination are negatively affected in patients with impaired cognitive function and dementia (27). Therefore, individuals without cognitive impairment were included in our study, and there was no difference between the MMSE results in the groups.

Limitations

Our study has some limitations. Firstly, older adult living in community dwelling were evaluated, and our results cannot be generalized for all older adult. Secondly, the individuals included in our study are the older adult who live in the community and have good mental status. Since it is predicted that the balance and physical performance of especially older adult with cognitive problems may be affected more, the effects of comorbidity on these older adult should be investigated in future studies. However, even older adults such as sarcopenia, frailty and osteosarcopenia were not included in our study. Future studies involving large elderly populations are needed to compare the effect of comorbidity on the timed limb coordination in healthy and sarcopenia, frail older adults.

CONCLUSION

The supination-pronation test, finger to nose test, knee to heel test results were better in low comorbidity level group in community-dwelling older adults. Coordination is very important in providing postural control and balance, and as a result of its deficiency, there is an increase in the risk of falling. Falling in older adult is an important problem that occurs as a result of a deficiency in the postural control system due to a specific pathology or ageing. Therefore, exercise training is extremely important in evaluating coordination and maintaining balance and reducing the risk of falling in older adult. It may be important to investigate the effects

of rehabilitation and exercise programs in reducing the negative features of comorbidity in future studies. In conclusion, as the comorbidity levels of older adult increase, regular evaluation and follow-ups are required in terms of timed limb coordination. These individuals need preventive physiotherapy and rehabilitation practices to increase their independence in physical functions. Thus, as the level of comorbidity increases, physiotherapy and rehabilitation practices become more necessary. It is thought that, in older adults with chronic diseases, physiotherapy and rehabilitation programs to improve physical and functional capacity, exercises which increase the level of physical activity level, balance and coordination will play an important role in improving physical performance.

Main Points

- Timed limb coordination for upper and lower limb were better in low comorbidity level group in community-dwelling older adults.
- The comorbidity levels of older adult must be evaluated and follow-ups are required in terms of timed limb coordination.
- These individuals need preventive physiotherapy and rehabilitation practices to improve timed limb coordination.

ETHICAL DECLARATIONS

Ethics Committee Approval: or the study, ethical consent was received from the Non-Interventional Research Ethics Committee of Kırıkkale University (Date: 26.08.2020., Decision No: 2020.07.03).

Informed Consent: All individuals included in the study were informed in detail about the purpose and methodology of the study, and their consent for participation in the study was obtained

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. Smith SM, Wallace E, O'Dowd T, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database Syst Rev 2016; 3: Cd006560.
2. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet (Eng) 2012; 380: 37-43.
3. Glynn LG, Valderas JM, Healy P, et al. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. Fam Pract 2011; 28: 516-23.
4. Salive ME. Multimorbidity in older adults. Epidemiol Rev 2013; 35: 75-83.
5. Botes R, Vermeulen KM, Correia J, Buskens E, Janssen F. Relative contribution of various chronic diseases and multi-morbidity to potential disability among Dutch elderly. BMC Health Serv Res 2018; 18: 24.
6. Rueda-Delgado LM, Solesio-Jofre E, Serrien DJ, Mantini D, Daffertshofer A, Swinnen SP. Understanding bimanual coordination across small time scales from an electrophysiological perspective. Neurosci Biobehav Rev 2014; 47: 614-35.
7. Serrien DJ, Swinnen SP, Stelmach GE. Age-related deterioration of coordinated interlimb behavior. J Gerontol B Psychol Sci Soc Sci 2000; 55: P295-303.
8. Shumway-Cook A, Woollacott MH. Motor control: translating research into clinical practice: Lippincott Williams & Wilkins; 2007.
9. Hollman JH, Conner MN, Goodman KA, Kremer KH, Petkus MT, Lanzino DJ. Timed limb coordination performance is associated with walking speed in healthy older adults: a cross-sectional exploratory study. Gait Posture 2013; 38: 316-20.
10. Lanzino DJ, Conner MN, Goodman KA, Kremer KH, Petkus MT, Hollman JH. Values for timed limb coordination tests in a sample of healthy older adults. Age Ageing 2012; 41: 803-7.
11. Ryan A, Murphy C, Boland F, Galvin R, Smith SM. What is the impact of physical activity and physical function on the development of multimorbidity in older adults over time? a population-based cohort study. J Gerontol A Biol Sci Med Sci 2018; 73: 1538-44.
12. Charlson M, Wells MT, Ullman R, King F, Shmukler C. The Charlson comorbidity index can be used prospectively to identify patients who will incur high future costs. PloS one 2014; 9: e112479.
13. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975; 12: 189-98.
14. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. Standardize mini mental test'in Türk toplumunda hafif demans tanısında geçerlik ve güvenilirliği. Türk Psikiyatri Derg 2002; 13: 273-81.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-83.
16. Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. Am J Med 2000; 108: 609-13.
17. Mirelman A, Bernad-Elazari H, Nobel T, et al. Effects of aging on arm swing during gait: the role of gait speed and dual tasking. PloS one 2015; 10: e0136043.
18. James EG, Leveille SG, Hausdorff JM, et al. Rhythmic interlimb coordination impairments and the risk for developing mobility limitations. J Gerontol A Biol Sci Med Sci 2017; 72: 1143-8.
19. Heuninckx S, Wenderoth N, Debaere F, Peeters R, Swinnen SP. Neural basis of aging: the penetration of cognition into action control. J Neurosci 2005; 25: 6787-96.
20. Capranica L, Tessitore A, Olivieri B, Minganti C, Pesce C. Field evaluation of cycled coupled movements of hand and foot in older individuals. Gerontology 2004; 50: 399-406.
21. Margolis JF, Christina RW. A test of Schmidt's schema theory of discrete motor skill learning. Res Q Exerc Sport 1981; 52: 474-83.

22. de Rugy A, Montagne G, Buekers MJ, Laurent M. The control of human locomotor pointing under restricted informational conditions. Neurosci Lett 2000; 281: 87-90.
23. James EG, Leveille SG, Hausdorff JM, et al. Rhythmic Interlimb Coordination Impairments Are Associated With Mobility Limitations Among Older Adults. Exp Aging Res 2017; 43: 337-45.
24. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. J Gerontol A Biol Sci Med Sci 2013; 68: 39-46.
25. National Guideline Centre (UK). Multimorbidity: Assessment, Prioritisation and Management of Care for People with Commonly Occurring Multimorbidity. London: National Institute for Health and Care Excellence (UK); September 2016.
26. Ortiz PJ, Tello T, Aliaga EG, et al. Effect of multimorbidity on gait speed in well-functioning older people: A population-based study in Peru. Geriatr Gerontol Int 2018; 18: 293-300.
27. Franssen EH, Souren LE, Torossian CL, Reisberg B. Equilibrium and limb coordination in mild cognitive impairment and mild Alzheimer's disease. J Am Geriatr Soc 1999; 47: 463-9.

Original Article

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Evaluation of serum perlecan levels in pregnancy with mild and severe preeclampsia

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ABSTRACT

Aim: To determine the levels of perlecan contributing to angiogenesis and autophagy inhibition in severe and mild preeclamptic women.

Material and Method: The study included a total of 89 patients as 3 group including severe preeclampsia as group 1 (n:30), mild preeclampsia as group 2 (n:30), and control as group 3 (n:29). All the groups were evaluated in terms of prepartum maternal serum perlecan levels.

Results: The Perlecan level of the group 1 was at higher levels than others ($p<0.0001$). The Perlecan level in the group 2 was higher than the control ($p<0.0001$). In the correlation analysis, AST ($p<0.0001$), ALT ($p<0.0001$), systolic blood pressure ($p<0.0001$), diastolic blood pressure ($p<0.0001$), creatinine ($p<0.0001$), proteinuria ($p<0.0001$), and LDH ($p<0.0001$) were positively correlated with perlecan level in the severe preeclampsia.

Conclusion: Serum perlecan levels were higher in preeclamptic pregnant women and this increased more especially in those with severe preeclampsia clinic.

Keywords: Perlecan, preeclampsia, autophagy, angiogenesis, pathophysiology

INTRODUCTION

Preeclampsia, characterized by hypertension and proteinuria, is one of the most important clinical conditions during pregnancy (1). It is seen in 3-5% of all pregnancies worldwide and seriously affects the life of the mother and baby (2).

Various factors have been suggested in studies investigating the conditions that prevent the development of the placental bed (3). There are crucial factors in the pathogenesis of preeclampsia such as systemic inflammation, hormonal and biochemical changes in the placenta, increase and decrease of proteins in maternal blood (4). Uteroplacental circulatory failure that develops as a result of placental dysfunction in the first trimester plays a critical role in its pathogenesis (5). Placental dysfunction reduces the invasion of trophoblasts into the decidua, and this decrease causes maternal hyperdynamic circulation and endothelial activation by causing villus hyperplasia, placental hypoperfusion, and vasopressor release by causing modification in spiral arteries (6,7).

Hypoxia occurring at the physiological level causes trophoblast invasion in the early period of placenta formation by affecting autophagy at the basal level (8). Autophagy reduces the aggregation of proteins in cells, that is, it has a protective effect on the cell; by inhibiting autophagy, proteins such as the amyloid increase in the cell and impair cell function (9). The findings explaining the relationship between preeclampsia and autophagy are still controversial.

In that term, Perlecan, a derivative of heparan sulfate, one of the main components of the basement membrane, comes to the fore because it increased angiogenesis and reduced autophagy according to the recent studies (10-12). Furthermore, perlecan level increases from the 17th week to the 40th week of pregnancy, but although its physiological role in pregnancy is not known exactly (13).

The present study aimed to analyze preaclampsia in separate groups and measured the prepartum perlecan levels in maternal serum to investigate its effect in preeclampsia.

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MATERIAL AND METHOD

Study Design

The study was designed as a level-II prospective observational clinical research and performed after the approval by Clinical Research Ethics Committee of Kahramanmaraş Sütçü İmam University, Faculty of Medicine (Date: 29/08/2018, Decision No: 06, Session: 2018/5). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The written informed consents were obtained from the patients.

The study included a total of 89 patients who admitted to the Gynecology and Obstetrics Department on 2019 to 2020 as 3 group including severe preeclampsia as group 1 (n:30), mild preeclampsia as group 2 (n:30), and control as group 3 (n:29). All the groups were evaluated in terms of prepartum maternal serum perlecan levels.

Inclusion/Exclusion Criteria

Patients with 20 to 36 pregnancy weeks were included in the study. Patients with blood pressure above 140/90 mmHg and with proteinuria more than 300 mg/l in 24-hour urine were included in the mild preeclampsia group. In addition, those with blood pressure above 160/110 mmHg, those with more than twice as high AST and ALT values, those with creatinine value above 1.1 mg/dl, those with thrombocyte count less than 100,000 µl, those with pulmonary edema, those with epigastric pain and with no other diagnosis, those with a new-onset headache non-responsive to drugs, and those with visual symptoms were included in the severe preeclampsia group. Patients whose gestational week were compatible with the patients in the other group and who did not have chronic hypertension, gestational hypertension, gestational diabetes mellitus, renal disease, autoimmune disease, and multiple pregnancies were included in the control group.

Definitions of Preeclampsia

Mild preeclampsia: New onset blood pressure is 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic. Proteinuria is 300 mg/24 hours; or ≥1+ on 2 random urine samples, collected at least 4 hours apart or protein: creatinine ratio is ≥0.3 mg/dL. In the absence of proteinuria, the following factors should be present: thrombocytopenia with platelets count <100,000/uL; serum creatinine ≥1.1 mg/L or a doubling of the serum creatinine concentration in the absence of another renal disease; impaired liver function with elevated blood concentrations of liver transaminases to twice normal concentration. In addition to them; Pulmonary oedema, Cerebral or visual disturbances,

Severe preeclampsia: BP is ≥160 mmHg systolic and/or ≥110 mmHg diastolic on two occasions and taken at least six hours apart or Proteinuria is 300 mg/24 hours; or ≥1+ on 2 random urine samples, collected at least 4 hours apart or protein: creatinine ratio is ≥0.3 mg/dL. In the absence of proteinuria, the following factors should be present: thrombocytopenia with platelets count <100000/ul, serum creatinine ≥1.1 mg/l or a doubling of the serum creatinine levels in the absence of another renal disease, the impaired liver function as indicated by elevated blood levels of liver transaminases to twice the normal concentration, pulmonary oedema, cerebral or visual disturbances.

Clinical Measurements

The gestational ages of the patients at the time of diagnosis were confirmed by the first-trimester crown-rump length and the last menstrual period. Gravida and the parity of all patients included in the study were questioned. Body mass indexes were calculated through height and weight measurements (kg/m^2). Their systolic and diastolic blood pressure values were recorded.

Laboratory Analysis

Proteinuria values were determined in 24-hour urine. Hemogram, AST, ALT, creatinine, uric acid, and LDH were tested. In addition, venous blood samples were taken from the antecubital area by phlebotomy method to simultaneously see the perlecan level of patients. The blood sample tubes were kept in an upright position for 10-20 minutes for coagulation and then centrifuged at +4°C and 4000 rpm for 10 minutes. Serum samples obtained were aliquoted and placed in the deep freezer at -80°C and kept until the day of analysis. On the day, when all serum samples were at room temperature, measurements were made using the enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions. (BOSTER antibody and ELISA experts, Human Endorepellin/HSP2 ELISA Kit PicoKineTM Catalog number: EK1760, Boster Biological Technology, USA). Detection range of the kit was 0.624-40 ng/mL and detection sensitivity was <0.05 ng/mL.

Statistical Assessments

The collected patient data were analyzed using the Statistical Package For Social Sciences - SPSS for Windows 23.0 package (IBM Statistical Package, New York, USA). Mean and standard deviation were given as descriptive values for continuous data and variables with normal distribution, and the median for non-normally distributed variables. For comparisons between groups, the "ANOVA Test" was used for more than two groups in normally distributed variables, and the "Kruskal Wallis

H-Test" was used for more than two groups in non-normally distributed variables. Post-Hoc Tukey test was used to determine which parameters the significance arose from in the evaluations that were found to be significant. the possible relation between labaratory parameters and serum perlecan level was investigated with spearman correlation test. Results were considered statistically significant in cases where the p-value was less than 0.05.

RESULTS

There was no significant difference between the three groups in terms of age, body mass index (BMI), gravida, and parity between the groups. All three groups were evaluated in terms of perlecan levels. Group 1's perlecan level was found higher than the other groups and this difference was statistically significant when compared with the other two groups. Compared with the control group, a significant increase was found in favor of Group 2. There was also a significant difference between the groups in terms of SBP and DBP. There was no significant difference between the groups in terms of hemoglobin and platelet values (p=0.555, p=0.056, respectively). While there was no significant difference in AST and ALT values between group 2 and group 3, a significantly higher difference was found between group 1 and the other groups. While there was no significant difference between group 1 and group 2 in terms of creatinine values, a significant difference was observed between these groups and the control group. While there was no difference between group 1 and group 2 in terms of LDH and uric acid values, a significant difference was detected between these groups and the control group. In terms of proteinuria, significant differences were found between group 1 and group 2, between group 1 and the control group, and between group 2 and the control group (**Table 1**). In terms of correlation of perlecan levels in groups with hematological parameters, it was observed that perlecan level was positively correlated with SBP, DBP, AST, ALT, creatinine, proteinuria, and LDH levels in Group 1. It was observed that perlecan levels of Group 2 were positively correlated with AST, ALT, creatinine, proteinuria, LDH, and uric acid levels and negatively correlated with platelet levels (**Table 2**). The distribution and mean value of perlecan levels among the groups were found to be 2.43 ng/mL in the severe preeclampsia group, 1.22 ng/mL in the mild preeclampsia group, and 0.89 ng/mL in the control group. The distribution range of perlecan level was very wide in the severe preeclampsia group, while it was narrow in the control group (**Figure**).

Table 2. Analysis results of the correlation of perlecan levels of groups with other hematological parameters

Characteristics	Severe preeclampsia		Mild preeclampsia		Control	
	R	p values	R	p value	R	p value
SBP	0.506	*0.004*	0.322	0.082	0.087	0.653
DBP	0.594	*0.001*	0.321	0.083	0.107	0.580
Hb	0.104	0.585	0.169	0.373	0.352	0.061
Platelet	-0.286	0.125	-0.414	*0.023*	0.345	0.067
AST	0.755	*<0.0001*	0.429	*0.018*	0.326	0.084
ALT	0.697	*<0.0001*	0.423	*0.020*	0.285	0.134
Creatinine	0.554	*0.001*	0.412	*0.024*	0.171	0.376
Proteinuria	0.457	*0.011*	0.478	*0.008*	-0.242	0.205
LDH	0.619	*<0.0001*	0.385	*0.035*	0.176	0.361
Uric Acid	0.312	0.093	0.386	*0.035*	0.233	0.224

s: Spearman correlation analysis. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hb: Hemoglobin

Table 1. Distribution of demographic and clinical findings by groups

Characteristics	Total (n:89)	Severe Preeclampsia (Group 1) (n=30)	Mild Preeclampsia (Group 2) (n=30)	Control (n=29)	p-value
Age (year)	27 (15)	27 (15)	27 (13)	25 (14)	0.547
BMI (kg/m^2)	23.9 (20.2)	26.2 (20.2)	23.9 (16.2)	23.7 (18)	0.655
Gestational age (weeks)	32 (13)	33 (11)	31 (12)	32 (10)	0.188
Gravidity	2 (5)	2 (4)	2 (5)	2 (5)	0.995
Parity	1 (4)	0.5 (4)	1 (4)	1 (4)	0.997
Perlecan level (ng/ml)	1.22 (5.97)	2.43 (5.56)	1.22 (3.07)	0.89 (1.24)	*<0.0001*^{k}
SBP (mmHg)	145 (176)	164.5 (136)	148.5 (18)	113 (45)	*<0.0001*^{k}
DBP (mmHg)	92.28±18.4	107.5±17.4	95.36±7.1	73.27±7.95	*<0.0001*^{a}
Hb (gr/dl)	10.75±1.34	10.91±1.48	10.54±1.4	10.8±1.1	0.555
Platelet (10^3/μL)	214.3±67.5	194.5±69.7	212.7±68.7	236.4±58.9	0.056
AST (U/L)	19 (256)	29 (254)	19 (27)	18 (19)	*<0.0001*^{k}
ALT (U/L)	12 (258)	25.5 (257)	8.5 (27)	11 (25)	*<0.0001*^{k}
Creatinine (mg/dL)	0.53 (1.06)	0.65 (0.99)	0.54 (0.62)	0.42 (0.41)	*<0.0001*^{k}
Proteinuria (gr/day)	566 (4997)	1057 (4630)	709.5 (2808)	93 (159)	*<0.0001*^{k}
LDH (U/L)	214 (508)	273.5 (507)	255 (364)	144 (150)	*<0.0001*^{k}
Uric acid (mg/dl)	4.88±2.44	6.06±2.8	4.93±2.1	3.62±1.68	*<0.0001*^{a}

All the data were given as Mean±SD or Median (Clearance). a: Anova test, k: Kruskal Wallis test. BMI: Body mass index, Hb: Hemoglobin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

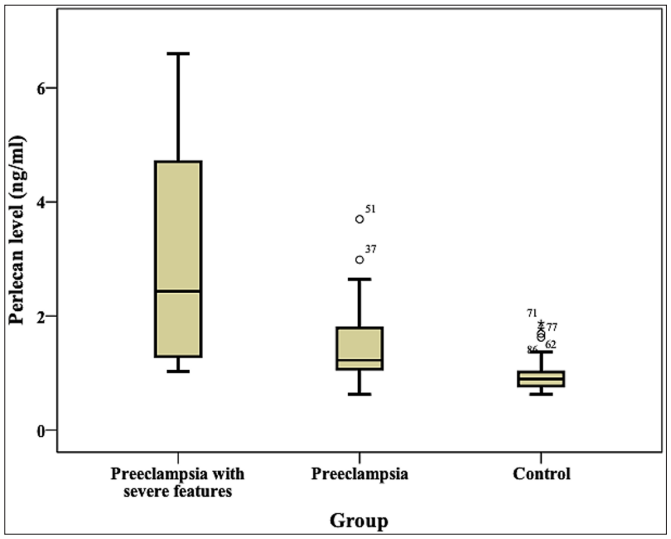

Figure. Distribution of perlecan levels between groups and their mean values

DISCUSSION

In our study, we found that the perlecan level was higher in the severe and mild preeclampsia group than in the control group. In addition, we found that perlecan level increased in the severe preeclampsia group in proportion to systolic and diastolic blood pressures, liver and kidney function tests.

In the study of Akbaş et al. (14) another study similar to our study, perlecan level was found to be high in severe preeclampsia cases. This study is important as it is a preliminary study that suggests that perlecan may play a role in the pathogenesis of preeclampsia. However, that study differs from our study in that the perlecan level was found to be high only in severe preeclampsia cases and a significant increase was not found in mild preeclampsia cases. In this study, we considered that perlecan level may be different in cases of preeclampsia and this may be due to the effects of proteoglycans on placental development and regulation of autophagy. The high perlecan level in both mild and severe preeclampsia cases we observed in our study supports the idea that perlecan may play a role in the pathogenesis of preeclampsia. In addition, the increased perlecan level in the severe preeclampsia group in proportion to systolic and diastolic blood pressures and liver and kidney function tests suggests that there may be a relationship between preeclampsia severity and perlecan level. It is possible to consider that as the severity of preeclampsia increases, the severity of autophagy, which is shown to be responsible for the pathogenesis process, also increases and the level of perlecan increases as a defense mechanism that prevents it.

Although Szenasi et al. (15) found increased perlecan levels in early preeclampsia in a similar study, they did not detect an increase in perlecan levels in late preeclampsia. In this study, it was concluded that the pathology of early preeclampsia was caused by abnormal trophoblast invasion-ischemic damage-placental stress, whereas late preeclampsia was based on a different pathology. In this study, it was found that the perlecan level decreased as the gestation period progressed. Yang et al. (16) found that perlecan level decreased as gestational age progressed, and perlecan level increased as gestational age progressed in those with gestational diabetes. In this study, hyperglycemia increased the level of perlecan. Confirming the information obtained from these studies, the high level of perlecan in preeclampsia suggests that perlecan is secreted as a defense molecule against abnormal processes in the body. It is a protective molecule and its level increases as a response to the abnormal autophagic reaction known to play a role in the pathogenesis of preeclampsia.

In another study for preeclampsia cases, it has been found that mRNA and protein expression of perlecan was significantly reduced. Perlecan has an angiogenesis-inducing effect and a decrease in perlecan level contributes to the pathogenesis of preeclampsia by reducing trophoblast invasion (17). Another study conducted to determine biological markers in cases with premature rupture of membranes found that perlecan level did not decrease in amniotic fluid, and although the role of heparan sulfate-derived proteoglycans in amniotic fluid is not known precisely, it has been considered to have a growth factor-like effect (13).

In a study by Zhao et al. (18) they showed that inhibition of protein kinase C beta increases autophagic activity and this increase triggers preeclampsia in both humans and animals. Recent studies report that the same inhibition triggers autophagy in preeclampsia after it has been shown that histone deacetylase inhibition triggers autophagy in multiple myeloma (19). Other studies report that autophagy activation is also associated with the enhancement of immune response and this affects the pathogenesis of preeclampsia (20). Similarly, we found the increased level of perlecan , although no evidence had about autophagy in our study. When the literature is reviewed, despite the findings of previous studies that inhibition of autophagy triggers preeclampsia, recent studies suggest that the increase in autophagy is more effective in the pathogenesis of preeclampsia (4).

A small number of patients and the lack of shorter gestational weeks are the limiting factors of our study. Besides, we should mention absence of placental level evaluation, absence of the parturition data, absence of umblical cord blood level and absence of the relation between perlecan level and neonate birthweight and APGAR score in the present study.

CONCLUSION

The maternal serum perlecan level was higher in the severe and mild preeclampsia group than in the control. In addition, perlecan level increased in the severe preeclampsia group in proportion to systolic and diastolic blood pressures, liver and kidney function tests. Based on the findings we obtained from our study consider that perlecan may be biochemical for understanding preeclampsia cases. Findings of the present study will be a guide for further studies to explain the relationship between perlecan and preeclampsia.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from Clinical Research Ethics Committee of Kahramanmaraş Sütçü İmam University, Faculty of Medicine (Date: 29/08/2018, Decision No: 06, Session: 2018/5).

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. El-Sayed AAF. Preeclampsia: A review of the pathogenesis and possible management strategies based on its pathophysiological derangements. Taiwanese J Obstet Gynecol 2017; 56: 593-8.
2. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol 2013; 170: 1-7.
3. Oh SY, Hwang JR, Choi M, et al. Autophagy regulates trophoblast invasion by targeting NF-κB activity. Scientific Reports Sci Rep.2020; 10: 14033.
4. Nakashima A, Aoki A, Kusabiraki T, Cheng SB, Sharma S, Saito S. Autophagy regulation in preeclampsia: Pros and cons. Journal of Reproductive Immunology 2017; 123: 17-23.
5. Karumanchi SA, Bdolah Y. Hypoxia and sFlt-1 in preeclampsia: the "chickenand-egg" question, Endocrinology 2004; 145: 4835-7.
6. Smets EML, Visser, Go ATJI, Vugt JMGV, Oudejans CBM. Novel biomarkers in preeclampsia. Clin Chim Acta 2006; 364: 22-32.
7. Ramos JGL, Sass N, Costa SHM. Preeclampsia. Rev Bras Ginecol Obstet 2017; 39: 496-512.
8. Nakashima A, Yamanaka-Tatematsu M, Fujita N, et al. Impaired autophagy by soluble endoglin, under physiological hypoxia in early pregnant period, is involved in poor placentation in preeclampsia. Autophagy 2013; 9: 303-16.
9. Kalkat M, Garcia J, Ebrahimi J, et al. Placental autophagy regulation by the BOK-MCL1 rheostat. Autophagy 2013; 9: 2140-53.
10. Jiang X, Couchman JR. Perlecan and tumor angiogenesis. J Histochem Cytochem 2003; 51: 1393-410.
11. Ning L, Xu Z, Furuya N, Nonaka R, Yamada Y, Arikawa-Hirasawa E. Perlecan inhibits autophagy to maintain muscle homeostasis in mouse soleus muscle, Matrix Biol 2015; 48: 26-35.
12. Gubbiotti MA, Neill T, Iozzo RV. A current view of perlecan in physiology and pathology: A mosaic of functions. Matrix Biol 2017; 57-58: 285-98.
13. Vuadens F, Benay C, Crettaz D, et al. Identification of biologic markers of the prematüre rupture of fetal membranes: Proteomic approach. Proteomics 2003; 3: 1521-5.
14. Akbas M, Koyuncu FM, Ulkumen BA, Taneli F, Ozdemir H. Maternal serum perlecan levels in women with preeclampsia. Hypertens Pregnancy 2020; 39: 70-6.
15. Szenasi NL, Toth E, Balogh A, et al. Proteomic identification of membrane-associated placental protein 4 (MP4) as perlecan and characterization of its placental expression in normal and pathologic pregnancies. PeerJ 2019; 7: e6982.
16. Yang WC, Su TH, Yang YC, Chang SC, Chen CY, Chen CP. Altered perlecan expression in placental development and gestational diabetes mellitus. Placenta 2005; 26: 780–8.
17. Chui A, Murthi P, Brennecke SP, Ignjatovic V, Monagle PT, Said JM. The expression of placental proteoglycans in pre-eclampsia. Gynecol Obstet Invest 2012; 73: 277-84.
18. Zhao H, Gong L, Wu S, et al. The inhibition of protein kinase C β contributes to the pathogenesis of peeclampsia by activating autophagy. EBioMedicine 2020; 56: 102813.
19. Du J, Ji Q, Dong L, Meng Y, Xin G. HDAC4 Knockdown Induces Preeclampsia Cell Autophagy and Apoptosis by miR-29b. Reprod Sci 2021; 28: 334-42.
20. Cornelius DC, Wallace K. Autophagy in preeclampsia: A new target? EBioMedicine 2020; 57: 102864.
21. Wu PH, Lin YT, Chiu YW, et al. The relationship of indoxyl sulfate and p-cresyl sulfate with target cardiovascular proteins in hemodialysis patients. Sci Rep 2021; 11: 3786.
22. Melrose J. Perlecan, a modular instructive proteoglycan with diverse functional properties. Int J Biochem Cell Biol 2020; 128: 105849.
23. Jansson M, Billing O, Herdenberg C, et al. Expression and circulating levels of perlecan in breast cancer-implications for oestrogen dependent stromal remodeling. J Mammary Gland Biol Neoplasia 2020; 25: 69-77.
24. Mishra M, Chandavarkar V, Naik VV, Kale AD. An immunohistochemical study of basement membrane heparan sulfate proteoglycan (perlecan) in oral epithelial dysplasia and squamous cell carcinoma. JOMFP, 2013; 17: 31-5.
25. Elgundi Z, Papanicolaou M, Major G, et al. Cancer metastasis: the role of the extracellular matrix and the heparan sulfate proteoglycan perlecan. Front Oncol 2020; 9: 1482.

Original Article

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Evaluation of factors affecting 90-day mortality in patients hospitalized due to pulmonary thromboembolism

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ABSTRACT

Aim: Pulmonary thromboembolism (PTE) is a leading cause of death from vascular events. In the pathophysiology of PTE, inflammatory mediators have been shown to be upregulated and to interact with coagulation factors. In this study, we aimed to investigate the role of symptoms, clinical and radiological findings, and the blood parameters measured at presentation within the first 24 h after the onset of the symptoms in predicting 90-day mortality and intensive care unit (ICU) requirement in patients with PTE.

Material and Method: The retrospective study included 264 PTE patients that were followed up at our Chest Diseases clinic and ICU between 2014 and 2019.

Results: The 264 patients comprised 55.3% women and 44.7% men with a mean age of 62.80±15.95 years. Of these, 189 of them were hospitalized in the Chest Diseases clinic and the remaining 75 patients were followed up at ICU. Total mortality occurred in 8 (3%) out of 264 patients. Hospital and ICU mortality were determined at 1.9% , 1.1% respectively. The patients comprised 206 (78.0%) nonmassive PTE, 17 (6.5%) submassive PTE, and 41 (15.5%) massive PTE. Risk factors for 90-mortality included white blood cell count (WBC), red blood cell distribution width (RDW), mean platelet volume (MPV)/RDW ratio, right ventricular dilatation (RVD), recombinant tissue plasminogen activator (rtPA) therapy, ICU hospitalization, and increased APACHE II (Acute Physiology and Chronic Health Evaluation II) scores ($p<0.05$).

Conclusion: The results indicated that TTE findings, baseline hemodynamic parameters and symptoms, rtPA therapy, and CBC parameters including WBC, NE, and RDW are significant risk factors for predicting both mortality and ICU requirement.

Keywords: Pulmonary embolism, inflammatory, mortality

INTRODUCTION

In acute PTE, early diagnosis and treatment are of prime importance in the reduction of mortality, and the mortality rates range from 0.3 to 12 per 100 diagnoses (1-3). Right ventricular dilatation (RVD) is partially associated with early mortality and can be evaluated by transthoracic echocardiography (TTE) and spiral thoracic computed tomography pulmonary angiography (CTPA). In the pathophysiology of PTE, inflammatory mediators have been shown to be upregulated and serum levels of inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6) have been shown to be elevated within 48 h after the onset of acute thrombosis (4).

Red blood cell distribution width (RDW), mean platelet volume (MPV), total neutrophil count (NE), and total lymphocyte count (LY) are inexpensive and standard biomarkers routinely measured in complete blood count (CBC). The percentage of serum RDW typically increases in hemoglobinopathies associated with iron deficiency. Additionally, recent clinical studies indicated that the percentage of serum RDW also increases in patients with increased oxidative stress and inflammation (5). On the other hand, RDW has been shown to be a useful marker in the diagnosis and prediction of prognosis and mortality in PTE patients. MPV, which is also measured in CBC, represents average platelet size and correlates with platelet function and activation. Although the MPV level in bone marrow may decrease or increase depending on the levels of inflammatory cytokines, it remains unknown as to which conditions cause increased or decreased serum MPV levels (6). Additionally, although serum MPV levels have been shown to be higher in patients with deep vein

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thrombosis (DVT) compared to control subjects, there is no standardization in the literature regarding serum levels of MPV in PTE patients (7). In the presence of inflammation, NE is increased while LY is decreased as a result of elevated cortisol levels caused by the activation of sympathetic system. Moreover, both the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been shown to be higher in PTE patients compared to non-PTE individuals (8,9).

The present study was designed to investigate the role of symptoms, clinical and TTE findings, and the blood parameters measured at presentation in predicting 90-day mortality and intensive care unit (ICU) requirement in patients that were diagnosed with PTE in our emergency service and then referred to the Chest Diseases clinic or ICU for treatment within the first 24 h after presentation.

MATERIAL AND METHOD

The retrospective study included 264 PTE patients that were followed up at our Chest Diseases clinic and intensive care unit (ICU) between 2014 and 2019. After obtaining an ethical approval from the Pamukkale University Non-interventional Clinical Research Ethics Committee (Date: 21.05.2019, Decision No: 10). Health Sciences University, Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Specialization in Medicine Education Board approval (Date: 27.02.2020, Decision No: 664). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patient records, ICU observation charts, and plain radiographic images were retrieved from hospital databases and were reviewed for each patient. All the patients included in the study initially presented to our emergency service and were transferred to the chest diseases clinic or ICU within the first 24 h after presentation, underwent CBC examination at presentation, and were initiated on 90-day mortality follow-up and on appropriate treatments in accordance with international guidelines. Additionally, the findings of both CTPA and 2-point compression ultrasonography of the lower extremity (USG) were evaluated by an experienced radiologist and the diagnosis of PTE was established by an experienced cardiologist based on TTE findings. Due to our retrospective study, USG could not be standardized. At the same time, it could not be repeated in the 3-5-7 days recommended in the guidelines for the diagnosis of DVT (1). The TTE findings were classified in terms of RVD, paradoxical septal motion with left-axis deviation, and pulmonary artery pressure (PAP). Based on hemodynamic monitoring findings, a heart rate of 50-100 beats/min was accepted as normal, >100 beats/min as tachycardia, and <50 beats/min as bradycardia. In noninvasive arterial blood pressure, a systolic blood pressure (SBP) of 90-120 mmHg was accepted as normotensive, a >20 mmHg increase in SBP compared to baseline values or a SBP of >120 mmHg was accepted as hypertension, and a ≤40 mmHg decrease in SBP within 15 min compared to baseline values or a SBP of <90 mmHg was accepted as hypotension.Oxygen saturation measured by pulse oximetry (SpO_2) >90% was considered as normal. SpO_2<90% was accepted as hypoxemia (1,2). Exclusion criteria were as follow: pregnancy, age below 18 years, signs of active infection, chronic kidney disease, malignancies, connective tissue disease, ongoing anticoagulant therapy, myocardial infarction, hematological malignances, history of blood transfusion within the last one month, thyroid disease, low iron, vitamin B12, and folic acid levels, and an ongoing treatment. CTPA was performed using a 128-slice CT device (slice thickness, 0.6 mm) (Definition AS, Siemens Medical Solutions, Forchheim, Germany). CBC parameters were measured by the photometric method on a Mindray BC-800 autoanalyzer. Normal ranges of CBC parameters including white blood cell count (WBC), hemoglobin (HB), hematocrit (HCT), platelet count (PLT), RDW, NE, LY, and MPV were accepted as 4.6-10.2 $10^3/\mu L$, 12-16 g/dL, 40-54%, 142-424 $10^3/\mu L$, 11.6-17.2%, 2-7 $10^3/\mu L$, 0.8-4 $10^3/\mu L$, and 7.8-11 fL, respectively. Based on CBC measurements, NLR, PLR, and the MPV/PLT and MPV/RDW ratios were calculated for each patient.

Statistical Analysis

Data were summarized as mean±standard deviation and median (Range) for continuous variables, frequencies (percentiles) for categorical variables.Student's test or Mann Whitney U test was used for independent group comparisons,depending on the distributional properties of the data.Chi-square test was used for proportions and its counterpart Fisher's Exact test was used when the data were sparse. All analyses were performed IBM SPSS Statistics for Windows, Version 20.0. A p value <0.05 was considered as statistically significant.

RESULTS

The 264 patients comprised 146 (55.3%) women and 118 (44.7%) men with a mean age of 62.80±15.95 years. Of these, 189 (71.6%) of them were hospitalized in the Chest Diseases clinic and the remaining 75 (28.4%) patients were followed up at ICU. In the patients that were hospitalized in ICU, the mean APACHE II (Acute Physiology and Chronic Health Evaluation II) score was 21.40±5.42 (**Table 1**). **Table 2** presents the findings of CTPA and 2-point compression ultrasonography of the lower extremity.

On TTE examination, RVD was detected in 124 (47.0%) and paradoxical septal motion with left-axis deviation was detected in 19 (7.3%) patients, and the mean PAP was 45.90±15.01 mmHg. **Table 3** presents the TTE findings for Chest Disease and ICU clinic.

Table 1. Demographic and clinical characteristics

Variables		Chest Disease Clinic Mean ± SD	ICU Mean ± SD	Total Mean ± SD	p
Age		62.69 ± 15.85	63.07 ± 16.31	62.80 ± 15.95	0.864
Variables		**Chest Diseases Clinic (n, %)**	**ICU (n, %)**	**Total (n, %)**	**p**
Gender	Female	105 (71.9)	41 (28.1)	146 (55.3)	0.896
	Male	84 (71.2)	34 (28.8)	118 (44.7)	
Comorbidities	No	93 (75.6)	30 (24.4)	123 (46.6)	0.176
	Yes	96 (68.1)	45 (31.9)	141 (53.4)	
DM	No	170 (72.3)	65 (27.7)	235 (89.0)	0.442
	Yes	19 (65.5)	10 (34.5)	29 (11.0)	
CAD	No	142 (73.6)	51 (26.4)	193 (73.1)	0.239
	Yes	47 (66.2)	24 (33.8)	71 (26.9)	
CHF	No	172 (72.3	66 (27.7)	238 (90.2)	0.460
	Yes	17 (65.4)	9 (34.6)	26 (9.8)	
AF	No	181 (71.3)	73 (28.7)	254 (93.9)	0.548
	Yes	8 (80.0)	2 (20.0)	10 (6.1)	
COPD	No	145 (69.4)	64 (30.6)	209 (79.2)	0.120
	Yes	44 (23.3)	11 (14.7)	55 (20.8)	
Dyspnea	No	25 (51.0)	24 (49.0)	49 (18.6)	<0.001
	Yes	164 (76.3)	51 (23.7)	215 (81.4)	
Fever	No	156 (72.2)	60 (27.8)	216 (81.8)	0.629
	Yes	33 (68.8)	15 (31.3)	48 (18.2)	
Dry cough	No	156 (75.7)	50 (24.3)	206 (78.0)	0.005
	Yes	33 (68.8)	15 (31.3)	48 (18.2)	
Hemoptysis	No	158 (72.8))	59 (27.2)	217 (82.2)	0.345
	Yes	31 (66.0)	16 (34.0)	47 (17.8)	
Chest pain	No	139 (73.2)	51 (26.8)	190 (82.2)	0.366
	Yes	50 (67.6)	24 (32.4)	74 (28.0)	
Risk factor	No	119 (82.6)	25 (17.4)	144 (54.5)	<0.001
	Yes	70 (58.3)	50 (41.7)	120 (44.5)	
Genetic risk factor	No	186 (71.3)	75 (28.7)	261 (98.9)	0.272
	Yes	3 (100.0)	0 (0.0)	3 (11.0)	
Acquired risk factor	No	119 (83.2)	24 (16.8)	143 (54.2)	<0.001
	Yes	70 (57.9)	51 (42.1)	121 (81.4)	
Variables			**n**	**%**	
Mechanical ventilation		No	236	89.4	
		NIV	13	4.92	
		IMV	15	5.68	
Mortality (90 days)		No	256	97.0	
		Yes	8	3.0	
Hospital Mortality		No	261	98.9	
		Yes	3	1.1	
ICU Mortality		No	259	98.1	
		Yes	5	1.9	
Acute PTE		Nonmassive	206	78.0	
		Massive	41	15.5	
		Submassive	17	6.5	
SSBP (mmHg)		Normotensive (SBP 90-120 mmHg)	216	81.8	
		Hypertensive (SBP >120 mmHg or >20 mmHg increase compared to baseline)	4	1.51	
		Hypotensive (SBP <90 mmHg or a ≤40 mmHG decrease in SBP within 15 min compared to baseline)	44	16.7	
Heart rate (beats/min)		Normal (50-100 beats/min)	124	47.0	
		Tachycardic (>100 beats/min)	131	49.6	
		Bradycardic (<50 beats/min)	9	3.4	
SpO_2 (%)		Normal (>%90)	97	36.7	
		Hypoxemic (<%90)	167	63.3	

DM:Diabetes mellitus, CAD:Coronary artery disease, CHF:Congestive heart failure, AF:Atrial fibrillation, COPD:Chronic obstructive pulmonary disease SBP:Systolic blood pressure, NIV:Noninvasive mechanical ventilation, IMV:Invasive mechanical ventilation, SpO2: Oxygen saturation measured by pulse oximetry, ICU:Intensive care unit,SD: Standard deviation, PTE: Pulmonary thromboembolism.

Table 2. Radiological findings

Variables		Frequency	Percentage
USG	Left DVT	33	12.5
	Right DVT	14	5.3
	Bilateral DVT	7	2.7
	Right main femoral vein DVT	10	3.8
	Left main femoral vein DVT	7	2.7
	Right iliac+femoral vein DVT	1	0.4
	Right main femoral vein+left DVT	1	0.4
	Bilateral iliocaval DVT	1	0.4
	Left iliac vein DVT	1	0.4
	No DVT	186	70.5
	Total	264	100.0
CTPA	Main pulmonary artery thrombus	14	5.3
	Bilateral main pulmonary artery thrombus	27	10.2
	Bilateral segmental artery thrombus	7	2.7
	Bilateral subsegmental artery thrombus	94	35.6
	Right main pulmonary artery thrombus	20	7.6
	Right subsegmental artery thrombus	67	25.4
	Left main pulmonary artery thrombus	5	1.9
	Left subsegmental artery thrombus	25	9.5
	Right main pulmonary+left subclavian artery thrombus	1	0.4
	Right main pulmonary+left subsegmental artery thrombus	1	0.4
	Total	261	98.9

USG:2-point compression ultrasonography of the lower extremity, CTPA:Spiral thoracic computed tomography pulmonary angiography, DVT:Deep vein thrombosis

Table 3. Transthoracic echocardiography findings

Variables		Chest Diseases Clinic (Mean±SD)	ICU (Mean±SD)	Total (Mean±SD)	p
PAP		42.50±13.73 mmHg	51.53±15.43 mmHg	45.90±15.01 mmHg	<0.001
			Mean±SD		**p**
PAP	Thrombolytic therapy (rtPA)		53.75±15.41 mmHg		<0.001
	LMWH		42.53±13.64 mmHg		
	Half-dose thrombolytic therapy (rtPA) (50 mg)		50.63±13.52 mmHg		0.156
	Full-dose thrombolytic therapy (rtPA) (100 mg)		56.98±17.95 mmHg		
		Chest Diseases Clinic (n, %)	**ICU (n, %)**	**Total (n, %)**	**p**
RVD	No	125 (72.3)	15 (10.7)	140 (53.0)	<0.001
	Yes	60 (48.4)	64 (51.6)	124 (47.0)	
Paradoxical septal motion with left-axis deviation	No	185 (76.1)	58 (23.9)	243 (92.7)	<0.001
	Yes	4 (21.1)	15 (78.9)	19 (7.3)	
		Half-dose thrombolytic therapy (rtPA) (50 mg) (n, %)	**Full-dose thrombolytic therapy (rtPA) (100 mg) (n, %)**	**Total (n, %)**	
RVD	No	4(80.0)	1(20.0)	5(8.8)	0.157
	Yes	21(40.4)	31(59.6)	57(91.2)	

RVD:Right ventricular dilatation, PAP:Pulmonary artery pressure, rtPA:Recombinant tissue plasminogen activator, LMWH:Low-molecular-weight heparin, SD: standard deviation

The patients comprised 206 (78.0%) nonmassive, 17 (6.5%) submassive, and 41(15.5%) massive acute PTE (**Table 1**).Of the 264 patients, 57 (21.6%) of them received rtPA and 207 (78.4%) of them received LMWH therapy. In the rtPA group, 25 (43.9%) of them received half-dose rtPA therapy (50 mg) and 32 (56.1%) of them received full-dose rtPA therapy (100 mg). Treatment-related complications were observed in 14 (5.4%) of 264 patients, including 7 (3.4%) patients in the LMWH group and 7 (13.0%) patients in the rtPA group.

Table 4 presents complete blood count parameters. Total mortality occurred in 8 (3.0%) out of 264 patients. Hospital and ICU mortality were determined at 1.9% , 1.1% respectively (**Table 1**).Risk factors for 90-mortality included comorbidities, acquired risk factors, ICU hospitalization, increased APACHE II scores, presence of RVD on TTE, rtPA therapy, invasive and noninvasive mechanical ventilation, and persistent hypotension, tachycardia, and hypoxemia (p=0.008,p=0.025,p=0.001 ,p<0.001, p=0.028, p=0.035, p<0.001, p=0.001, p<0.001,

p=0.028). Of these parameters, WBC, RDW, and MPV/RDW ratio were found to be significant risk factors for 90-day mortality (p=0.032, p=0.041, and p=0.039) (**Table 5**).

Risk factors for ICU requirement included acquired risk factors, dyspnea, dry cough, syncope, presence of RVD on TTE, paradoxical septal motion with left-axis deviation, PAP, rtPA therapy, invasive and noninvasive mechanical ventilation, use of vasopressors, and persistent hypotension and hypoxemia (p<0.001). Additionally, baseline CBC parameters including WBC, HB, HCT, RDW, and NE were also found to be significant factors for ICU requirement (**Table 6**).

Table 4. Complete blood count parameters

Variables	Mean±SD	Median (DW)
WBC (10^3/μL)	10.07±3.82	21.00 (25.00)
HB (g/dL)	13.27±1.91	13.30 (12.60)
HCT (%)	39.91±5.76	40.00 (38.30)
PLT (μL)	269227.27±95667.25	254000.00 (672000.00)
RDW (%)	15.15±2.12	14.60 (13.80)
NE (10^3/μL)	7.30±3.65	6.39 (21.81)
LY (10^3/μL)	1.92±1.28	1.71 (12.60)
MPV (fL)	8.31±1.25	8.30 (14.17)
NE/LY ratio	5.83±7.40	3.57 (77.21)
PLT/LY ratio	188234.83±149730.06	155044.93 (175000.00)
MPV/PLT ratio	0.0000349±0.0000138	0.0000327 (0.0000724)
MPV/RDW ratio	0.56±0.11	0.55 (1.03)

WBC:White blood cell count, HB:Hemoglobin, HCT:Hematocrit, PLT:Platelet count, RDW:Red blood cell distribution width, NE:Neutrophil count, LY:Lymphocyte count, MPV:Mean platelet volume, SD: Standard deviation

Table 5. Risk factors for mortality

Variables	No mortality occurred			Mortality occurred			p
	n	Mean±SD	Median(DW)	n	Mean±SD	Median (DW)	
Age	256	62.58±1.59	63.00 (73.00)	8	69.75±14.88	72.00 (44.00)	0.212
APACHE II	256	20.70±5.00	20.00 (24.00)	8	28.71±3.64	28.00 (11.00)	<0.001
PAP	256	46.67±15.15	42.00 (87.00)	8	51.43±10.29	50.00 (30.00)	0.322
Duration of ICU stay (days)	256	3.71±3.27	3.00 (21.00)	8	5.00±8.02	2.00 (22.00)	0.404
Duration of stay at clinic (days)	256	8.62±6.75	7.00 (88.00)	8	4.13±7.36	0.00 (17.00)	0.065
WBC (10^3/μL)	256	9.98±3.70	9.30 (23.35)	8	12.93±6.28	11.10 (20.20)	0.032
HB (g/dL)	256	13.29±1.90	13.40 (12.60)	8	12.65±2.27	11.80 (6.90)	0.354
HCT (%)	256	40.01±5.67	40.10 (38.30)	8	36.69±7.89	34.20 (25.00)	0.108
PLT (μL)	256	270664.06±96458.89	255000 (672000)	8	223250.00±49271.12	218000.00(157000.00)	0.168
RDW (%)	256	15.10±2.12	14.60 (13.80)	8	16.66±1.93	16.80 (5.40)	0.041
NE (10^3/μL)	256	7.22±3.55	6.32 (19.51)	8	9.71±6.02	7.53 (18.90)	0.058
LY (10^3/μL)	256	1.91±1.22	1.74 (12.60)	8	2.23±2.54	1.45 (7.82)	0.490
fL	256	8.32±1.25	8.30 (14.17)	8	7.90±1.14	8.20 (3.10)	0.352
NE/LY ratio	256	5.69±7.05	3.56 (77.21)	8	10.37±14.95	5.75 (45.57)	0.078
PLT/LY ratio	256	188373.40±150855.91	155044 (175000.00)	8	183800.83±115198.63	169500.00(341484.15)	0.932
MPV/PLT ratio	256	0.00±0.00	0.00 (0.00)	8	0.00±0.00	0.00 (0.00)	0.741
MPV/RDW ratio	256	0.56±0.11	0.55 (1.03)	8	0.48±0.08	0.47 (0.25)	0.039

APACHE II:Acute Physiology and Chronic Health Evaluation II, PAP:Pulmonary artery pressure, ICU:Intensive care unit, WBC:White blood cell count, HB:Hemoglobin, HCT:Hematocrit, PLT:Platelet count,RDW:Red blood cell distribution width, NE:Neutrophil count,LY:Lymphocyte count, MPV:Mean platelet volume, SD: Standard deviation

Table 6. Risk factors for ICU requirement

Variables	No ICU required		ICU required		p
	Mean±SD	Median (DW)	Mean±SD	Median (DW)	
Age	62.70±15.90	62.00 (71.00)	63.04±16.21	66.00 (70.00)	0.877
PAP	42.24±13.53	40.00 (87.00)	51.81±15.49	50.00 (60.00)	<0.001
WBC (10^3/μL)	9.53±3.52	9.05 (22.90)	11.41±4.21	11.25 (23.05)	<0.001
HB (g/dL)	13.44±1.82	13.50 (12.60)	12.84±2.07	12.85 (9.60)	0.021
HCT (%)	40.37±5.44	40.15 (38.30)	38.76±6.39	38.90 (32.00)	0.039
PLT (μL)	275723.40±97467.55	257000.00 (672000.00)	253157.89±89665.31	227500.00(437000.00)	0.083
RDW (%)	14.97±2.14	14.50 (13.80)	15.59±2.04	15.05 (9.90)	0.032
NE (10^3/μL)	6.74±3.32	6.10 (19.40)	8.68±4.07	7.94 (21.81)	<0.001
LY (10^3/μL)	1.92±1.27	1.80 (12.50)	1.93±1.30	1.55 (8.13)	0.925
MPV (fL)	8.30±1.16	8.30 (10.45)	8.33±1.45	8.43 (9.17)	0.842
NE/LY ratio	5.28±5.85	3.41 (45.71)	7.19±10.20	4.50 (76.66)	0.059
PLT/LY ratio	186749.15±119104.04	154810.04 (982500.00)	191909.94±207911.52	155061.63(1737310.92)	0.8
MPV/PLT ratio	0.00±0.00	0.00 (0.00)	0.00±0.00	0.00 (0.00)	0.132
MPV/RDW ratio	0.56±0.11	0.55 (0.78)	0.55±0.13	0.55 (0.72)	0.268

PAB:Pulmonary artery pressure, ICU:Intensive care unit, WBC:White blood cell count, HB:Hemoglobin, HCT:Hematocrit, PLT:Platelet count, RDW:Red blood cell distribution width, NE:Neutrophil count, LY:Lymphocyte count, MPV:Mean platelet volume, SD: Standard deviation

DISCUSSION

Risk factors for 90-mortality included WBC, RDW, MPV/RDW ratio, comorbidities, acquired risk factors, ICU hospitalization, increased APACHE II scores, presence of RVD on TTE, rtPA therapy, invasive and noninvasive mechanical ventilation, and persistent hypotension, tachycardia, and hypoxemia.

In Acute PTE, the mechanical obstruction of the pulmonary vascular bed caused by a thrombus localized to the pulmonary arteries leads to hemodynamic alterations, thereby leading to increased ventricular afterload and often resulting in RVD and hypokinesia. TTE is a bedside diagnostic tool commonly used in the detection of RVD and in making systemic thrombolytic treatment decisions (9). A previous study retrospectively evaluated the TTE findings of patients with massive PTE and detected RVD in 90.0%, paradoxical septal motion with left-axis deviation in 65.0%, and PAP >40 mmHg in 60.0% of the patients (10). Similarly, Serra et al. (11) retrospectively evaluated the TTE findings of PTE patients and revealed the baseline PAP as 39 mmHg. In our study, RVD was detected in 53.0% and paradoxical septal motion with left-axis deviation was detected in 7.3% of the patients. The TTE findings of the patients were retrospectively reviewed by an experienced cardiologist and patients with ventricular dysfunction and heart valve disease were excluded from the study. The mean PAP was 45.90±15.01 mmHg, which was higher than most of the values reported in the literature. This difference was attributed to the high prevalence of systemic thrombolytic therapy in our patients who had hemodynamic instability or in those who were hemodynamically stable but had RVD (21.5%). Moreover, the mean PAP in our patients that were hospitalized in the Chest Diseases clinic was remarkably high (42.50±13.73 mmHg), which could be associated with the fact that the TTE findings were examined by different cardiologists and by using different devices and that the TTE findings are not standardized and thus can be affected by hemodynamic alterations such as body weight and tachycardia. As most of the patients hospitalized in ICU were hemodynamically instable, their TTE findings were statistically significant compared to those of patients who were hospitalized in the Chest Diseases clinic, as consistent with the literature.

Intravenous thrombolytic agents can be used to reduce pulmonary perfusion and PAP and to restore right ventricular function in a prompt manner (12,13). Current international guidelines propose that PTE patients with RVD and hemodynamic instability can be treated with systemic half-dose (rtPA 50 mg) or full-dose (rtPA 100 mg) thrombolytic therapy based on the benefit/loss analysis for each patient (14,15). In some studies, half-dose therapy has been shown to be as effective as full-dose therapy and has also been reported to promote angiographic revascularization and to provide an improvement in PAP similar to that of full-dose therapy. Streptokinase, urokinase, and rtPA are commonly used thrombolytic agents (16,17). In our study, 57 (21.5%) patients received rtPA as systemic thrombolytic therapy, among whom 25 (43.9%) patients received half-dose rtPA (50 mg) and 32 (56.1%) patients received full-dose rtPA (100 mg). Acute PTE is available in studies that indicate the systemic thrombolytic therapy reguirement 4.2% and 18.0% (16,17). In our study, however, the prevalence of systemic thrombolytic therapy was higher than those reported in the literature, which could be associated with several factors including the high rate of ICU hospitalization (28.4%), high APACHE II scores and PAP values, and high prevalence of vasopressor requirement, hemodynamic instability, and RVD in our patients. On the other hand, the prevalence of full-dose rtPA therapy was higher than that of half-dose rtPA therapy (56.1% vs. 43.9%) (11,16,17). However, no significant difference was found between these two groups with regard to PAP and the prevalence of RVD, both of which are significant pathfinders in the decision-making processes regarding thrombolytic therapy and its dosage. This finding could be attributed to the prioritization of hemodynamic findings over TTE findings in the decision-making processes regarding thrombolytic therapy and its dosage.

PTE is a significant cause of mortality and morbidity. In previous studies, 90-day mortality rate has been reported as 58.3% in patients with massive PTE and as 15.1% in patients with submassive PTE (11,18). In our study, massive (15.3%) and submassive (6.5%) PTE ratio has been lower than studies where 90 days of mortality have been evaluated.Hospital stay in patients with acute PTE has been reported to vary between 4 and 10 days (19,20). In our study, 90-day mortality occurred in 8 (3.0%) out of 264 patients. This rate was remarkably lower than those reported in the literature, which could be associated with the administration of systemic thrombolytic therapy in hemodynamically instable patients and the shorter duration of hospitalization among our ICU patients (3.83± 3.87 days). In our study, mean duration of hospital stay was 8.49±6.80 days and the mean duration of ICU stay was 3.83±3.87 days. In our study, the heterogeneous patient groups and the high number of nonmassive acute PTE patients (nonmassive, massive and submassive) caused the number of hospital stay days to be high. No significant difference was found between these two values (hospital and ICU stay days) with regard to 90-day mortality. In our study, it was thought that the data of patients without hemodynamic change may affect our results.Our results are compared to literature information in acute PTE, where 90 days mortality are evaluated. This finding could be associated with the low mortality

rate in our patients. Additionally, the duration of hospitalization in our ICU patients was lower than those of many studies in the literature. On the other hand, the longer hospitalization period in the patients hospitalized in the chest diseases clinic compared to the patients hospitalized in ICU could be ascribed to the fact that most of the patients that were initiated on the LMWH therapy subsequently used oral anticoagulants (warfarin) as maintenance therapy and the patients were discharged after ensuring patient compliance with the anticoagulant warfarin therapy. Risk factors for 90-mortality included comorbidities, acquired risk factors, ICU hospitalization, increased APACHE II scores, presence of RVD on TTE, rtPA therapy, invasive and noninvasive mechanical ventilation, and persistent hypotension, tachycardia, and hypoxemia.In contrast, risk factors for ICU requirement included acquired risk factors, dyspnea, dry cough, syncope, presence of RVD on TTE, paradoxical septal motion with left-axis deviation, PAP, rtPA therapy, invasive and noninvasive mechanical ventilation, use of vasopressors, and persistent hypotension and hypoxemia. Taken together, these findings implicate that hemodynamic parameters were risk factors for both mortality and ICU requirement, as consistent with the literature.

In the pathophysiology of PTE, inflammatory mediators have been shown to be upregulated and to interact with coagulation factors. There is no cellular infiltration in the pulmonary artery during the acute stage while leukocyte infiltration occurs within the subsequent three hours and two days, which decreases on the fourth day and returns to baseline levels on the eighth day (18). Inflammatory markers including WBC, HB, NE, LY, PLT, RDW, and MPV, which are inexpensive and standard biomarkers that are routinely measured in CBC, have recently become a major research area in the evaluation of PTE (21,22). In those studies, serum levels of these markers have been shown to decrease or increase in PTE. Additionally, increased NE counts have been associated with subclinical inflammation and decreased LY counts have been attributed to the elevated glucocorticoid levels induced by sympathetic activation (22). They are used either in isolation or in ratios such as NE/LY and PLT/LY ratios for predicting mortality and risk factors in acute PTE. A previous review suggested that the NE/LY ratio could be used in predicting mortality in PTE patients although there are some studies presenting controversial results regarding the use of NE/LY and PLT/LY ratios in such predictions (23). PLT plays a central role in thromboembolic diseases by secreting prothrombotic and proinflammatory molecules. MPV is a biomarker which represents average platelet size and has been shown to indicate macrothrombocytes when elevated and to play a role in venous thrombosis (24). RDW reflects the degree of heterogeneity of RBC size and has been shown to be elevated in conditions leading to increased levels of inflammatory markers such as CRP. Additionally, an elevated RDW indicates immature RBC production in the bone marrow and is known to be associated with the changes in blood viscosity and acute inflammation (25,26). In a previous case-control study, Payman et al. (27) evaluated 173 PTE patients and reported that the PLT counts were not elevated in any patient. In contrast, another study evaluated patients with acute DVT and reported that the MPV/PLT ratio and the MPV values were higher in the patients compared to control subjects (28). Kovacs et al. (7) reviewed multiple studies that evaluated DVT patients and revealed that the MPV values were significantly elevated in the patients compared to control subjects and this elevation was found to be statistically significant in patients with acute PTE in subgroup analyses. Some other studies suggested that MPV is an independent risk factor in predicting early mortality in acute PTE (28,29). Similarly, a prospective study evaluated 378 patients with acute PTE and reported that baseline RDW value was an independent risk factor for predicting 17-month mortality (30). Some previous studies proposed low MPV and RDW values for predicting thrombus risk and mortality while some others proposed high values, serial measurements, and different cutoff values for different groups of the same disease In our study, baseline serum parameters were measured in CBC and the NE/LY, PLT/LY, MPV/PLT, and MPV/RDW ratios were calculated based on these parameters (31). We used these parameters and ratios to investigate their role in predicting 90-day mortality and ICU requirement. The measurements indicated that although the NE and WBC counts were higher than the reference values, no significant decrease was found in the LY counts, unlike in other studies (22). Moreover, WBC, NE, HB, HCT, and RDW were found to be significant risk factors for predicting ICU requirement and WBC, RDW, and the MPV/RDW ratio were significant risk factors for predicting 90-day mortality. Accordingly, RDW was found to be a significant risk factor for predicting both mortality and ICU requirement, which could be attributed to the high prevalence of hemodynamic instability, blood viscosity changes, and acute inflammation in our patients. Additionally, the PLT, NE/LY, PLT/LY, and MPV/PLT ratios were insignificant risk factors and the PLT and LY counts were in normal ranges, which could be ascribed to numerous factors including the retrospective nature of the study, nonstandardization of the methods used in collecting baseline serum samples at hospital presentation (i.e. the absence of a fixed timing schedule for the collection of serum samples), failure to analyze

time-dependent biomarkers such as MPV within one hour after blood collection, and the absence of serial measurements. Accordingly, we consider that serial measurement of inflammatory markers at presentation (baseline) and at 3, 24, and 48 hours after presentation could have revealed an increase in these parameters and their ratios. This assumption is relies on the literature data that indicated that acute inflammation begins to increase three hours after the onset of the symptoms and remains elevated for up to 48 h (18). Accordingly, in our study, the mean WBC and NE values showed an early increase while the MPV, PLT, and LY values showed a normal increase, which could be explained by the fact that MPV, PLT, and LY typically begin to increase at a later period compared to WBC and NE. Based on these findings, we suggest that the levels of these parameters in acute PTE should be standardized by serial measurements. We also consider that RDW can be an early marker of ICU requirement and mortality in acute PTE and further studies involving risk analysis are needed to investigate the role of RDW in acute PTE.

CONCLUSION

The results indicated that TTE findings, baseline hemodynamic parameters and symptoms, rtPA therapy, and CBC parameters including WBC, NE, and RDW are significant risk factors for predicting both mortality and ICU requirement. Further studies are needed to investigate the role of RDW and the MPV/RDW ratio in the risk analysis of PTE and in patients with thrombus or those with a risk of thrombus development.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Pamukkale University Non-interventional Clinical Research Ethics Committee (Date: 21.05.2019, Decision No: 10). Health Sciences University, Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Specialization in Medicine Education Board approval (Date: 27.02.2020, Decision No: 664).

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. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019: 54.
2. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. J Am Coll Cardiol 2019; 74: 932-87.
3. Weitz JI, Chan NC. Novel antithrombotic strategies for treatment of venous thromboembolism. Blood 2020; 135: 351-9.
4. Zhou XY, Chen HL, Ni SS. Red cell distribution width in predicting 30-day mortality in patients with pulmonary embolism. J Crit Care 2017; 37: 197-201.
5. Agarval S. Red cell distribution width, inflammatory markers and cardiorespiratory fitness: Results from the National Health and Nutrition Examination Survey. Indian Heart J 2012; 64: 380-7.
6. Montagana M, Cervelin G, Meschi T, Lippi G. The role of red blood cell distribution width in cardiovascular and thrombotic disorders. Clin Chem Lab Med 2011; 50: 635-41.
7. Kovacs S, Csiki Z, Zsori KS, Shemirani AH. Characteristics of platelet count and size and diagnostic accuracy of mean platelet volUme in patients with venous thromboembolism. A systematic review and meta-analysis. Platelets 2019; 30: 139-47.
8. Falk E, Shah PK, Fuster V.Coronary plague disruption.Circulation 1995; 92: 657-71.
9. Ishaaya E, Tapson VF. Advances in the diagnosis of acute pulmonary embolism. F1000Res 2020; 9.
10. Lee K, Kwon O, Lee EJ, et al. Prognostic value of echocardiographic parameters for right ventricular function in patients with acute non-massive pulmonary embolism. Heart Vessels 2019; 34: 1187-95.
11. Serra W, Crisafulli E, Syerzellati N, et al. Transthoracic echocardiography and chest computed tomography arteriography in patients with acute pulmonary embolism: a two-year follow-up study. Respiration 2016; 92: 235-40.
12. Hepburn-Brown M, Darvall J, Hammerschlag G. Acute pulmonary embolism: a concise review of diagnosis and management. Intern Med J 2019; 49: 15-27.
13. Manuel A, Aufico A, Africanı R, et al. Clinical profile, management and outcomes of patients with pulmonary embolism: a retrospective tertiary centre study in Angola. Cardiovasc J A fr 2017; 28 356-61.
14. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020 ; 41: 522-29.
15. Quezada A, Jimenez D, Bikdeli B, et al. Systolic blood pressure and mortality in acute symptomatic pulmonary embolism. Int J Cardiol 2020; 302: 157-63.
16. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet 2016; 388: 3060-73.
17. Verma B, Singh AK. Use of reteplase for thrombolysis in patients with massive pulmonary embolism diagnosed by bedside transthoracic echocardiography: A retrospective study of safety and efficacy. J Family Med Prim Care 2019; 8: 3155-9.
18. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. Am J Med 1984; 76: 393-7.
19. Fanikos J, Rao A, Seger AC, et al. Hospital Costs of Acute Pulmonary Embolism. Am J Med 2013; 126: 127-32.

20. Donadini MP, Dentali F, Castellaneta M, et al. Pulmonary embolism prognostic factors and length of hospital stay: A cohort study. Thromb Res 2017; 156: 155-9.
21. Omar HR, Mirsaeidi M, Rashad R, et al. Association of serum albumin and severity of pulmonary embolism. Medicana (Kaunas) 2020; 9: 56.
22. Bazouki G, Letsas KP, Vlachos K, et al. Simple hematological predictors of AF recurrence in patients undergoing atrial fibrillation ablation. J Geriatr Cardiol 2019; 16: 671-5.
23. Galliazzo S, Nigro O, Bertü L, et al. Prognostic role of neutrophils to lymphocytes ratio in patients with acute pulmonary embolism: a systematic review and metaanalysis of the literatüre. Intern Emerg Med 2018; 13: 603-8.
24. Farah R, Nseir W, Kagansky D, Khamisy-Farah R. The role of neutrophil-lymphocyte ratio and mean platelet volüme in detecting patients with acute venous thromboembolism. J Clin Lab Anal 2020; 34: e23010.
25. Hammons L, Filopel J, Steiger D, Bondarsky E. A narrative review of red blood cell distribution width as a marker for pulmonary embolism. J Thromb Thrombolysis 2019 ; 48: 638-47.
26. Yu FT, Armstrong JK, Tripette J, Meiselman HJ, Cloutier G. A local increase in red blood cell aggreagation ca trigger deep vein thrombosis: evidence based on quantitative cellular ultrasound imaging. J Thromb Haemost 2011; 9: 481-8.
27. Moharamzadeh P, Rahmani F, Foroughifar S, Shahsavarinia K. Reliability of Platelet Indices for Diagnosing Pulmonary Embolism; a Brief Report. Adv J Emerg Med 2019; 3: e27.
28. Han JS, Park TS, Cho SY, Joh JH, Ahn HJ. Increased mean platelet volume and mean platelet volüme/platelet count ratio in Korean patients with deep vein thrombosis. Platelets 2013; 24: 590-3.
29. Kostrubiec M, Labyk A, Pedowska-Wloszek J, et al. Mean platelet volume predicts early death in acute pulmonary embolism. Heart 2010; 96: 460-5.
30. Kheirkman-Saberghadam S, Jenab Y, Ghoreyski-Hefzabad, et al. Association between elevated red blood cell distribution width and long-term mortality in acute pulmonary embolism.Turk J Med Sci 2018; 48: 318-23.
31. Han YQ, Yan L, Zhang L, et al. Red blood cell distribution width provides additional prognostic value beyond severity scores in adult critical illness. Clin Chim Acta 2019; 498: 62-6.

Original Article

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The effect of myometrial invasion and histological grade on lymph node metastasis in patient with early stage endometrium cancer

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ABSTRACT

Aim: Early detection of endometrial cancer is important for the prognosis of the disease. In our study, the effect of myometrial invasion and histological grade on lymph node metastasis was investigated in patient with early stage endometrium cancer .

Material and Method: A total of 249 patients from the last 10 years who underwent systemic lymphadenectomy for staging in our hospital were retrospectively examined. The pathologies of these patients were limited to the uterine corpus. The effect of histological grade of tumor and myometrial invasion on lymph node metastasis was evaluated statistically.

Results: The average lymph node collected from patients was 27.7 (11-78). Lymph node metastasis was detected in 4.1% of patients with histological grade 1-2 and <1/2 myometrial invasion. Lymph node metastasis was detected in 18.3% of patients with grade 1-2 tumors with myometrial invasion ≥1/2. Lymph node metastasis was detected in 11.1% of patients with myometrial invasion <1/2 and histological grade 3. Lymph node metastasis was detected in 27.3% of patients with myometrial invasion ≥1/2 and histological grade 3.

Conclusions: The most important findings of our study are that histological degree and myometrial invasion are common independent markers for retroperitoneal lymph node metastasis in early stage endometrium cancers and demonstrate the necessity of lymphadenectomy.

Keywords: Endometrium cancer, lymph node metastasis, staging, myometrial invasion

INTRODUCTION

Unlike most other cancers, the incidence of endometrial cancer (EC) and death rates associated with it are increasing (1). EC is the sixth most common cancer in women and the 14th leading cause of cancer deaths worldwide (2). Hysterectomy and bilateral salpingo-oophorectomy combined with extensive lymph node dissection are standard for staging most ECs (3). One of the most important prognostic factors in EC is the presence of extrauterine disease including pelvic and paraaortic lymph node metastases (LNM). Lymphadenectomy during hysterectomy can provide a therapeutic benefit by providing an accurate assessment of the extent of the disease (4). In addition, lymphadenectomy has been proven to increase the surgical time and increase the risk of surgery-related morbidity, lymphocyst and lymphedema formation (5). Approach to lymph node evaluation especially in patients with early stage EC is controversial (6,7). Many gynecological oncologists agree that women with "low risk" EC do not require routine lymphadenectomy, but the definition of "low risk" is still difficult (8). Two randomized studies have shown that routine lymphadenectomy does not affect survival in patients with low-risk EC (9,10). Despite these facts, routine lymph node dissection is strongly recommended by some experts in all women with EC, regardless of the presence or absence of suspected lymph nodes (11). In a survey of GOG (Gynecological Oncology Group) members, it was found that up to 35% of experts performed both pelvic and paraaortic lymphadenectomy for grade I EC (12). Various models have been proposed to estimate the likelihood of lymph

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node metastasis using histopathological parameters in women with EC. One of these models was described in a study conducted at the Mayo Clinic. Comprehensive lymphadenectomy was performed on 187 patients with low-risk EC as part of their surgical staging in that study. Only 9 (5%) of 187 people had LNM, if the tumor size was less than 2 cm, no patient with LNM was detected in the low-risk group (13). Many retrospective analyzes have shown similar results in patients with low-risk characteristics (6,14).

The aim of this study is to evaluate the risk of nodal metastasis in patients with EC, whose disease is apparently confined to the uterine corpus, using data from our ten-year EC experience.

MATERIAL AND METHOD

This study was approved by Selçuk University Local Ethics Committee (Date: 05.05.2021, Decision No: 2021/247). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 412 cases of EC who underwent surgical treatment between 2010 and 2019 in the Department of Obstetrics and Gynecology, Faculty of Medicine, Our University, were detected. The study population was formed with 249 patients whose disease was limited to the uterine corpus. According to the 2009 International Federation of Gynaecology and Obstetrics (FiGO) staging, the entire study group was in stage I. Endometrioid histological type, histological grade I-II-III, patients with EC who had undergone both pelvic and paraaortic lymphadenectomy and whose disease was apparently confined to the uterine corpus were considered as inclusion criterias. Non-endometrioid or mixed histology, disease involving the cervix, adnexa, or peritoneal cavity, and only pelvic lymphadenectomy or only paraaortic lymphadenectomy were determined as exclusion criterias. Patients without data on tumor invasion, size and histological grade were excluded. Clinico-pathological data of the patients were obtained from the computerized database of our hospital and performed in a retrospective study format. A flow chart of the study design is presented in Figure 1. All procedures were done by gynecologist oncologists. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, cytological sampling, pelvic and paraaortic lymphadenectomy were performed in all patients. The patients were divided into two groups according to lymph node involvement. The first group consisted of those with positive lymph nodes, and the second group consisted of those with negative lymph nodes. Then each group was divided into 4 subgroups within itself. The subgroups were defined as follows. 1. low grade (grade1-2) and less than 1/2 myometrial invasion; 2. low grade (grade1-2) and more than 1/2 myometrial invasion; 3. those with high grade (grade 3) and less than 1/2 myometrial invasion; 4. those with high grade (grade 3) and more than 1/2 myometrial invasion. In this study; Parameters determining high and low risk in endometrioid type cancers were analyzed separately. Clinical and pathological characteristics of the patients, age, histological subtype, grade, depth of myometrial invasion and presence of LNMs were evaluated.

Statistical Analysis

Statistical evaluation was performed using the SPSS 20 (Statistical Package for Social Sciences) for Windows (IBM SPSS Inc., Chicago, IL) program. The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Among the numerical variables, those with normal distribution were shown as mean ± standard deviation, and those without normal distribution were shown as the median (min-max). Categorical variables were expressed as numbers and percentages.

RESULTS

A total of 249 patients who were operated with a diagnosis of EC in our hospital and whose disease was found limited to the uterine corpus according to the final pathology result were included in the study. The median age of the cases was found to be 59 (33-88 years). Tumor type was endometrioid type in 249 patients (100%). The median number of pregnancies was 3 (0-8). Although 12 patients (4.8%) never gave birth, 28 patients (11.2%) had 5 or more pregnancies. The first presentation symptom was vaginal bleeding in 229 patients (91.9%). While there was no myometrial invasion (MI) in 185 of the patients (74.3%), it was found that the tumor had spread up to the serosa in 64 (25.7%) of them. The rates of grade I, II, III patients were 168 (67.5%), 61 (24.5%), 20 (8%), respectively. The main characteristics of patients with endometrioid EC whose disease were apparently limited to the uterine corpus, are summarized in **Table 1**. The median lymph nodes number was 33.0 and ranged from 4 to 91. This number was 15.7 (range: 1-55) for the paraaortic area and 26 (range: 4-71) for the pelvic area. LNM was observed in 22 (8.8%) patients. Pelvic and pelvic+paraaortic LNM rates were 4% and 3.6%, respectively. The isolated paraaortic LNM rate was 1.2%. When factors affecting LNMs are evaluated, LNM was detected in 4.1% of patients with grade 1-2 tumors and <1/2 MI. LNM was detected in 18.3% of patients with grade 1-2 tumors with MI ≥1/2. LNM was detected in 11.1% of patients with grade 3 tumors with MI below 50%, and in 27.3% of patients with MI above 50%. LNM patterns of the patients are summarized in **Table 2**.

Table 1. The main characteristics of patients with endometrioid endometrial cancer whose disease were apparently limited to the uterine corpus

Mean Age±SD (Range)	59.38±10.44	(33-88)
Median Gravida ±SD (Range)	3.0±2.14	(0-8)
Median Lymph Node Number±SD (Range)	33.0±16.86	(4-91)
Median Pelvic Lymph Node Number±SD (Range)	26.0±12.44	(4-71)
Median Paraaortic Lymph Node Number±SD (Range)	15.7±23.12	(1-55)
Grade	**n**	**%**
1	168	67.5
2	61	24.5
3	20	8.0
Myometrial Invasion (MI)	**n**	**%**
<1/2 MI	185	74.3
≥1/2 MI	64	25.7

Table 2: Lymph node metastasis patterns of patients with endometrioid endometrial cancers whose disease were apparently limited to uterin corpus

	n	%
Lymph node metastasis		
No	227	91.2
Yes	22	8.8
Pattern of lymph node metastasis		
Only Pelvic LNM	10	4.0
Only Paraaortic LNM	3	1.2
Both Pelvic and Paraaortic LNM	9	3.6
Lymph node metastasis among patients with grade 1-2 tumor and <1/2 MI		
No	162	95.9
Yes	7	4.1
Lymph node metastasis pattern among patients with grade 1-2 tumor and <1/2 MI		
Only Pelvic LNM	2	1.2
Only Paraaortic LNM	3	1.8
Both Pelvic and Paraaortic LNM	2	1.2
Lymph node metastasis among patients with grade 1-2 tumor and ≥1/2 MI		
No	49	81.7
Yes	11	18.3
Lymph node metastasis pattern among patients with grade 1-2 tumor and ≥1/2 MI		
Only Pelvic LNM	5	8.3
Only Paraaortic LNM	0	0
Both Pelvic and Paraaortic LNM	6	10.0
Lymph node metastasis among patients with grade 3 tumor and <1/2 MI		
No	8	88.9
Yes	1	11.1
Lymph node metastasis pattern among patients with grade 3 tumor and <1/2 MI		
Only Pelvic LNM	1	11.1
Only Paraaortic LNM	0	0
Both Pelvic and Paraaortic LNM	0	0
Lymph node metastasis among patients with grade 3 tumor and ≥1/2 MI		
No	8	72.7
Yes	3	27.3
Lymph node metastasis pattern among patients with grade 3 tumor and ≥1/2 MI		
Only Pelvic LNM	2	18.2
Only Paraaortic LNM	0	0
Both Pelvic and Paraaortic LNM	1	9.1

LNM= Lymph Node Metastasis, MI= Myometrial Invasion

Table 3. Regression analysis of grade and myometrial invasion and lymph node involvement

	B	(β)	%95 CI	t	p
Grade	-0.096	0.335	0.13-0.89	-2.582	0.001
Myometrial invasion	0.051	0.386	-0.17-0.23	2.613	0.009

DISCUSSION

Staging of EC requires lymph node dissection, but the necessity and feasibility of lymphadenectomy is strongly debated. It is important to determine the risk factors that indicate that the disease may have spread to the lymph nodes in the preoperative or intraoperative period and performing lymphadenectomy in the patient group with these risk factors will be an appropriate surgical treatment option in EC. Studies have shown that low-risk EC patients generally have a small risk of LNM (14-17). Mariani et al. reported that patients with grade I, II histology, MI<50% and tumor size <2 cm are at a low risk for LNM. No LNM was found in that large cohort of 381 patients with low-risk EC (13). Given these findings, the authors of the study recommend postponing lymph node dissection in patients with low-risk endometrioid type EC. Similarly, the relationship between LNM and grade and depth of MI was tried to be evaluated in early stage ECs in the current study.

Grade is an important determinant for MI and LNM. As the differentiation degree of the tumor decreases, the risk of deep MI, LNM, local recurrence and distant metastasis increases (18). As the grade increases, a higher rate of LNM can be expected. Chi et al reported the rates of LNM as 4-17% in patients with grade 2 tumors (19). Mariani et al. reported that 7% of patients with grade II tumors had LNM (13). As such, we performed a similar analysis, our study supports previously published reports showing that the risk of LNM is low in patients with low grade. In the present study, LNM was observed in only 7 (4.1%) of 169 patients with grade I-II and <1/2 MI. It was observed that this parameter reached 11.1% for grade III and MI <1/2 tumors. Given these findings, it may be reasonable to postpone lymph node dissection in grade I-II tumors with less than 50% invasion.

The possibility of extrauterine spread and recurrence increases due to the ease of drainage into the lymphatic system in cases where the depth of invasion of the myometrium by tumoral tissues exceeds ½ ratio (20). This is the most important pathological finding that determines whether lymphadenectomy will be added to the surgery during the operation. MI is a criterion for the tumor to behave aggressively (21). The prediction of MI, which is an indication for pelvic and paraaortic lymph node dissection in EC, allows the surgery to be planned in advance. It has been determined that the depth of MI is more predictive than histopathological type and grade (22). Pelvic LNM

was reported to be 25% while paraaortic involvement was 17% in the presence of deep MI in a randomized controlled study (23). In Creasman's study, pelvic and paraaortic LNM was not observed in histologically grade I EC patients in the absence of MI (24). In our study, patients with MI limited to the endometrium or <50% were evaluated as no deep MI. The number of patients with both no deep MI and grade I-II was 169. Pelvic LNM was detected in 1.2 % of these patients, pelvic+paraaortic LNM was detected in 1.2% of patients and isolated paraaortic LNM was detected in 1.8% of the patients. There were 60 patients with grade I-II and deep MI (> 50%) and LNM was observed in 11 (18.3%) of 60 patients. The rate of pelvic LNM was 8.3%, pelvic+paraaortic LNM rate was 10% in these patients. Our findings are consistent with Creasman's study and reveal that deep MI plays an important role in the course of EC.

The study has limitations that must be taken into account when interpreting the data. First, this study is a retrospective review of a large database. Second, the factors that may be related to LNMs, such as tumor size and lymphovascular space invasion, have not been evaluated. Another limitation of the study is that no information was provided on overall survival and disease-free survival of patients in the study cohort.

CONCLUSION

The most important finding of our study is that grade and MI are common independent markers for retroperitoneal LNM in early stage ECs and indicate the necessity of lymphadenectomy. Therefore, high grade and deep MI are important factors that should suggest lymph node dissection for clinics who consider lymph node dissection unnecessary in early stage ECs.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Selçuk University Local Ethics Committee (Date: 15/04/2021, Decision No: 93).

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. Zengin M, Eryol M, Aydemir Akkaya M, Devrim T, Yalçın S, Özkan ZS. Did the terminology of endometrial intraepithelial neoplasia resolve the chaos in the classification of endometrial hyperplasia? a 8-year retrospective study. Anatolian Curr Med J 2020; 2; 129-35.
2. Njoku K, Abiola J, Russell J, Crosbie EJ. Endometrial cancer prevention in high-risk women. Best practice & research Clinical Obstetrics & Gynaecology 2020; 65: 66-78.
3. Braun MM, Overbeek-Wager E, Grumbo RJ. Diagnosis and management of endometrial cancer. Am Fam Physician 2016; 93: 468-74.
4. Chan JK, Cheung MK, Huh WK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. Cancer 2006; 107: 1823-30.
5. May K, Bryant A, Dickinson HO, Kehoe S, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev 2010; 1: CD007585.
6. Al Hilli MM, Podratz KC, Dowdy SC, et al. Preoperative biopsy and intraoperative tumor diameter predict lymph node dissemination in endometrial cancer. Gynecol Oncol 2013; 128: 294-9.
7. Kang S, Todo Y, Odagiri T, et al. A low-risk group for lymph node metastasis is accurately identified by Korean gynecologic oncology group criteria in two Japanese cohorts with endometrial cancer. Gynecol Oncol 2013; 129: 33-7.
8. Creasman WT. The current status of lymphadenectomy in the management of endometrial cancer. Women's Health (London, England) 2011; 7: 33-5.
9. Panici PB, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. JNCI: J National Cancer Institute 2008; 100: 1707-16.
10. Amant F, Neven P, Vergote I. Lymphadenectomy in endometrial cancer. The Lancet 2009; 373: 1169-70.
11. Carlson JW, Kauderer J, Hutson A, et al. GOG 244-The lymphedema and gynecologic cancer (LEG) study: Incidence and risk factors in newly diagnosed patients. Gynecol Oncol 2020; 156: 467-74.
12. Soliman PT, Frumovitz M, Spannuth W, et al. Lymphadenectomy during endometrial cancer staging: practice patterns among gynecologic oncologists. Gynecol Oncol 2010; 119: 291-4.
13. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol 2000; 182: 1506-19.
14. Convery PA, Cantrell LA, Di Santo N, et al. Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low-grade endometrial adenocarcinoma. Gynecol Oncol 2011; 123: 65-70.
15. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. Cancer 1987; 60: 2035-41.
16. Milam MR, Java J, Walker JL, et al. Nodal metastasis risk in endometrioid endometrial cancer. Obstet Gynecol 2012; 119: 286.
17. Shah C, Johnson EB, Everett E, et al. Does size matter? Tumor size and morphology as predictors of nodal status and recurrence in endometrial cancer. Gynecol Oncol 2005; 99: 564-70.
18. Kadar N, Malfetano JH, Homesley HD. Determinants of survival of surgically staged patients with endometrial carcinoma histologically confined to the uterus: implications for therapy. Obstet Gynecol 1992; 80: 655-9.
19. Chi D, Barakat R, Palayekar M, et al. The incidence of pelvic lymph node metastasis by FiGO staging for patients with adequately surgically staged endometrial adenocarcinoma of endometrioid histology. Int J Gynecol Cancer 2008; 18: 2.

20. Kaku T, Tsuruchi N, Tsukamoto N, Hirakawa T, Kamura T, Nakano H. Reassessment of myometrial invasion in endometrial carcinoma. Obstet Gynecol 1994; 84: 979-82.

21. Jantarasaengaram S, Praditphol N, Tansathit T, Vipupinyo C, Vairojanavong K. Three-dimensional ultrasound with volume contrast imaging for preoperative assessment of myometrial invasion and cervical involvement in women with endometrial cancer. Ultrasound in obstetrics & gynecology : the official J Int Soc Ultrasound Obstet Gynecol 2014; 43: 569-74.

22. Soliman PT, Frumovitz M, Spannuth W, et al. Lymphadenectomy during endometrial cancer staging: practice patterns among gynecologic oncologists. Gynecol Oncol 2010; 119: 291-4.

23. Benedetti Panici P, Basile S, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J National Cancer Institute 2008; 100: 1707-16.

24. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987; 60: 2035-41.

Original Article

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The predictive value of systemic immune inflammation index on long-term outcomes among acute pulmonary embolism patients

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ABSTRACT

Aim: The systemic immune inflammation index (SII) has begun to be used as a useful and new marker that predicts adverse clinical outcomes in patients with malignancies and cardiovascular diseases. We performed the present study assuming that SII could provide further additional information in predicting long-term mortality in patients with acute pulmonary embolism (APE).

Material and Method: We included 504 consecutive patients followed up with APE. The study group was divided into those survivors and non-survivors. Demographic, clinical, laboratory, and echocardiographic characteristics were compared between groups.

Results: A total of 28 (5.4%) patients died in the 30 days. Besides, during a clinical follow-up period of 29 [12-53] months, 52 patients (10.1%) died. According to the results of the regression analysis, age [odds ratio (OR): 1.052, 95% confidence interval (CI): 1.034–1.071; p<0.01], right ventricle end-diastolic diameter basal (OR: 3.227, 95% CI: 1.902–5.474; p<0.001), left ventricular ejection fraction (OR: 0.968, 95% CI: 0.948–0.988) and SII index (OR: 2.129, 95% CI: 1.290–3.515) were the independent predictors of overall mortality among the study population. A receiver operating characteristic curve analysis revealed that the area under the curve values of the SII index for overall mortality was 0.703 (95% CI: 0.629–0.777). SII with an optimal cutoff value of 1111×10^9 predicted the overall mortality with a sensitivity of 72% and specificity of 51%.

Conclusion: The SII index, an inexpensive and easily calculable parameter, was a strong predictor of overall mortality in patients with APE.

Keywords: Inflammatory marker, pulmonary embolism, risk assessment, systemic immune-inflammation index

INTRODUCTION

Patients diagnosed with acute pulmonary embolism (APE) constitute one of the leading causes of death among cardiovascular diseases., although mortality rates have declined effectively with early diagnosis and treatment (1). Inflammation plays a crucial role in pathogenesis in venous thromboembolism (VTE) (2).

Systemic inflammation has an important role in VTE risk stratification and can be evidenced by the detection of many circulating pro-inflammatory biomarkers (3). Many clinical trials exist on hematological parameters that can predict the clinical severity and survival of APE (4-7).

Clinical composite scores, echocardiographic parameters showing right ventricular (RV) strain have been proven in studies to predict short and long-term mortality (8-13). However, there is still a need for cheap and effective predictors of mortality that can be easily calculated in a short time.

The systemic immune-inflammation (SII) index was first used in patients with malignancy and proved to be an effective predictor of mortality (14). Subsequently, studies have been published that the same index may be effective in predicting mortality in patients with acute coronary syndrome and also in predicting the clinical severity of APE (15-18). To our knowledge, there is no study investigating the relationship between the SII index and long-term mortality among patients with APE in the literature. Hence, we sought to determine

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if a simple, routinely evaluated laboratory parameter at index hospital admission is practical for long-term risk stratification in patients with APE.

MATERIAL AND METHOD

Study Population

The study population included consecutive APE patients between January 2013 to December 2020 at 1 tertiary heart care center. A total of 856 patients were included in the study retrospectively from the medical records of our hospital. This study was approved by the Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.04.2021, Decision No: 2021/126). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients with a clinical diagnosis and documented by imaging criteria were included. The exclusion criteria were described as the existence of active or past malignancy, hematological disorders using an immunosuppressant medication, end-stage renal or hepatic failure, collagen vascular disease, and acute or chronic infection. Therewithal, patients who died within the first 24 hours after hospitalization as a consequence of massive APE and were, therefore, could not be evaluated by echocardiographic and laboratory examination were not recruited in the present study. The final study analysis was carried out by including a total of 514 patients.

Data Collection

Clinical symptoms, predisposing factors for VTE, demographic data, laboratory, and echocardiographic examinations of the recruited study participants were obtained using the hospital database. Patients were separated into the two groups as stated in survival status. The characteristics of the collected data were compared between the groups.

Pulmonary angiographic imaging with computed tomography (CTPA) was carried out on the whole study population with basal normal creatinine values to establish the diagnosis of APE. In cases where imaging with CTPA is not possible, the confirmation was verified by ventilation/perfusion lung scanning.

A detailed echocardiographic evaluation was performed on all patients which were included in the study during the first 24 hours after admission to evaluate their RV functions.

Evaluation of Echocardiographic Parameters

Echocardiographic analyses were done by using a device (vivid S5, GE Healthcare Systems, Chicago, Illinois, USA). The LV ejection fraction (LVEF) was measured via biplane two-dimensional Simpson's method. The maximum velocity of tricuspid regurgitation (TR-Vmax) was calculated from the apical four-chamber (A4C) view. The pressure of the right atrium (RA) was estimated from the inferior vena cava (IVC) thickness and in line with whether or not the IVC collapsed with respiration. The estimated pulmonary arterial systolic pressure (PASP) was measured as stated by the following formula: 4×TR-Vmax 2+estimated RA pressure. The end-diastolic diameters of RV (RV-EDDs) were measured from the RV-focused A4C at the basal segment.

Definitions and Study Outcomes

The SII index was calculated as total peripheral platelet counts (P)×neutrophil-to-lymphocyte ratio (N/L) (SII=P×N/L ratio) (14). A Pulmonary Embolism Severity Index (PESI) score calculation was performed for each patient by assessing 11 clinical variables, comprising demographics (age and sex), comorbidities (chronic lung disease, cancer, heart failure), and vital functions (systolic blood pressure, heart rate, respiratory rate, body temperature, arterial oxygen saturation and altered mental status) (8).

Diagnosis of deep vein thrombosis was confirmed with lower extremity Doppler venous ultrasonography. Hypertension (HT) was described as the current use of antihypertensive medication or initial blood pressure above 140/90 mmHg; diabetes mellitus (DM) was described as the use of anti-diabetic treatment or fasting glucose levels of >126 mg/dL and hyperlipidemia was described as total serum cholesterol levels of >240 mg/dL. Current smoking status was also defined.

The glomerular filtration rate (GFR) was computed using the Cockgraft- Gault equation (19).

Long-term mortality data were collected from the patient's medical records or domestic social security institution database. In cases where it is not possible to access this data, the current survival status of patients was verified by a phone conversation with the patient's family. The main outcome of the study was the occurrence of mortality at a 30-day period or long-term follow-up which was defined as all deaths from any cause.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences version 22.0 (IBM Corporation, Armonk, NY, USA). Continuous variables are given as mean±standard deviation or the median (interquartile range) values. Categorical variables are given as number (percentage) values. The Shapiro-

Wilk test was applied to assess normality. Normally distributed variables were compared between groups using an independent-samples t-test. Variables that do not fit the normal distribution were compared with the Mann–Whitney U test. Evaluation of categorical variables was done using the chi-squared or Fisher's exact test. Cox-regression analysis was performed to estimate predictive markers of long-term all-cause mortality. Receiver operating characteristic (ROC) curves were constituted to examine the ability of the SII index to predict 30-day, long-term, and overall mortality rates. The long-term survival status was established by the Kaplan–Meier method, and the log-rank test was used to assess differences between the two groups. A probability value of $p<0.05$ was considered to be statistically significant.

RESULTS

The study population included 514 patients, who were stratified according to their survival status. The mean age of the participants was 61.5±16.1. A total of 80 (15.6%) non-survivors and 434 (86.4%) survivors with APE were compared. Clinical, demographic characteristics, predisposing factors, echocardiographic parameters, and laboratory findings of the study population are provided in **Table 1,2,3**. History of DM and heart failure, the altered states of consciousness, fibrinolytic treatment were more prevalent among non-survivors. Age, PESI score, d-dimer levels, white blood cell, neutrophil, platelet count, and SII index were higher and GFR was lower among non-survivors. In terms of echocardiographic characteristics; RV-EDD and RVSP were significantly higher among non-survivors while those in survivors have higher LVEF.

Table 1. Baseline demographic and clinical characteristics regarding the patient groups.

	Study population (n=514)	Non-survivors (n=80)	Survivors (n=434)	P
Age, y, mean	61.5±16.1	71.2±14.1	59.7±15.8	**<0.001**[t]
Gender, female	282 (54.9)	46 (57.5)	236 (45.9)	0.606[x2]
Hypertension	294 (57.2)	53 (66.3)	241 (55.5)	0.075[x2]
Diabetes mellitus	145 (28.2)	30 (37.5)	115 (26.5)	**0.044**[x2]
Hyperlipidemia	119 (23.2)	20 (25)	99 (22.8)	0.670[x2]
Smoking	212 (41.2)	28 (35)	184 (42.4)	0.217[x2]
Previous heart failure	62 (12.1)	19 (23.8)	43 (9.9)	**<0.001**[x2]
Previous chronic kidney disease	47 (9.1)	7 (8.8)	40 (9.2)	0.894[x2]
Previous chronic obstructive pulmonary disease	81 (15.8)	15 (18.8)	66 (15.2)	0.424[x2]
Previous coronary artery disease	105 (20.4)	17 (21.3)	88 (20.3)	0.843[x2]
Blood pressure (systolic)	124±21.7	119.5±22.9	126±22	0.103[t]
Heart rate (bpm)	100.8±18.6	107.4±20.1	98.2±18	**0.008**[t]
PESI score	99.4±36.7	123±42.9	95.1±33.7	**<0.001**[t]
Day of hospital stay	8.2±5.4	7.1±5.6	8.4±5.4	0.05[t]
Main pulmonary artery involvement	167 (32.5)	42 (52.5)	125 (28.8)	0.193[x2]
Fibrinolytic therapy	132 (25.7)	32 (40)	90 (20.7)	**<0.001**[x2]
Follow-up (months)	29 (12-53)	9 (0-32)	35 (18-57)	-

x2 Chi-square; t independent-samples t-test; m Mann–Whitney U test, PESI: pulmonary embolism severity index, $p<0.05$ indicates statistical significance and was shown in bold characters.

Table 2. Comparison of symptoms and predisposing factors regarding the patient groups.

	Study population (n=514)	Non-survivors (n=80)	Survivors (n=434)	P
Predisposing factors				
Immobility for more than 3 days	68 (13.2)	15 (18.8)	53 (12.2)	0.113
Surgery in the last 1 month	32 (6.2)	7 (8.8)	25 (5.8)	0.309
Trauma within 2 months	22 (4.3)	1 (1.3)	21 (4.8)	0.145
Prior DVT/PE	31 (6)	9 (11.2)	22 (5.1)	0.125
Concomitant DVT	191 (37.2)	29 (36.3)	162 (37.3)	0.855
Symptoms				
Chest pain	98 (19.1)	10 (12.5)	88 (20.3)	0.104
Dyspnea	439 (85.4)	71 (88.8)	368 (84.8)	0.357
Syncope	114 (22.2)	15 (18.8)	99 (22.8)	0.422
Altered status of consciousness	23 (4.5)	7 (8.8)	16 (3.7)	**0.044**
Pain in the lower extremity	202 (39.3)	24 (30)	178 (41)	0.064

DVT, deep vein thrombosis; PE, pulmonary embolism, $p<0.05$ indicates statistical significance and was shown in bold characters.

Table 3. Comparison of echocardiographic characteristics and laboratory findings regarding the patient groups.

	Study population (n=514)	Non-survivors (n=80)	Survivors (n=434)	P
Echocardiographic parameters				
RV-EDD (A4C) (cm)	4±0.5	4.2±0.4	3.9±0.5	**<0.001**[t]
RVSP (mmHg)	50±12.5	51.4±16.4	49.8±11.7	0.283[t]
LVEF (%)	57.3±7.9	54.1±11	57.9±7	**0.004**[t]
Laboratory parameters				
Glucose, mg/dL	162±76.9	184.9±93.2	157.8±73	0.017[t]
Baseline Creatinine, mg/dL	1.15±0.63	1.19±0.4	1.15±0.66	0.625[t]
D-dimer (ng/mL)	2871 (1522-5587)	3278 (1716-8716)	2700 (1522-5466)	**0.031**[m]
Cardiac troponin (ng/mL)	0.33 (0.09-1.19)	0.32 (0.04-1.35)	0.33 (0.09-1.18)	0.605[m]
NT-proBNP (pg/dL)	318 (143-577)	320 (97-927)	318 (144-529)	0.986[m]
GFR, mL/min	66.6±25.4	59±23.4	68±25.6	**0.003**[t]
Hemoglobin, g/Dl	12.7±3.1	12.3±1.8	12.8±3.3	0.204[t]
WBC, $\times 10^9$/L	11.9±3.9	13.3±4.9	11.6±3.7	**0.004**[t]
Neutrophil, $\times 10^9$/L	9.1±3.3	10.5±4.2	8.9±3.1	**<0.001**[t]
Lymphocyte, $\times 10^9$/L	1.7±0.8	1.6±1.1	1.8±0.8	0.085[t]
Platelet, $\times 10^9$/L	230.4±78.2	251.4±81.9	226.5±77	**0.009**[t]
SII index	1193 (783-1769)	1918 (1032-3326)	1131 (769-1647)	**<0.001**[m]

t independent-samples t-test; m Mann–Whitney U test, A4C: apical four chamber; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP; N-Terminal-Pro-brain natriuretic peptide; PE,pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricle; RV-EDD, right ventricular end-diastolic diameter; RVSP, right ventricular systolic pressure; SII, systemic immune inflammation; WBC, white blood cell. p<0.05 indicates statistical significance and was shown in bold. characters.

While 28 (5.4%) of the patients included in the study died in the 30 days, during a follow-up period of 29 [12-53] months, 52 patients (10.1%) died. The overall mortality rate was 15.6%.

To identify independent predictors of overall mortality, we performed a Cox regression analysis of the whole study population. The univariate analysis revealed that age, DM, HT, GFR, RV-EDD, LVEF, WBC, neutrophil, lymphocyte, platelet count, and SII index were ascertained as potential independent predictors of overall mortality among patients with APE. In the multivariate regression analysis, age [odds ratio (OR): 1.052, 95% confidence interval (CI): 1.034–1.071; p<0.01], RV-EDD (OR: 3.227, 95% CI: 1.902–5.474; p<0.001), LVEF (OR: 0.968, 95% CI: 0.948–0.988) and SII index (OR: 2.129, 95% CI: 1.290–3.515) continued to exist being the independent overall mortality predictors among the study population (**Table 4**).

The SII index significantly predicted the rates of 30-day and long-term mortality as well as the rate of overall mortality. ROC analysis revealed that the provided area under the curve (AUC) values of the SII index for 30-day mortality, long-term, and overall mortality rates were 0.623 (95% CI: 0.504–0.742), 0.724 (95% CI: 0.634–0.813) and 0.703 (95% CI: 0.629–0.777), respectively (**Figures 1a-c**).

SII index>1111x109 cut-off value predicted overall mortality with a sensitivity of 72% and a specificity of 51%. Additionally, the Kaplan–Meier curve for patients with SII index over the cut-off values had a significantly higher risk for overall mortality (90.9% vs 79.1%, respectively, log-rank test p value<0.001) (**Figure 2**).

Table 4. Univariate and multivariate cox-regression analysis for all-cause mortality in patients with pulmonary embolism.

Univariate analysis	P	OR (95% CI)	Multivariate analysis	P	OR (95% CI)
Age	**<0.001**	1.052 (1.035-1.070)	Age	**<0.001**	1.052 (1.034-1.071)
Gender (Female)	0.535	0.869 (0.558-1.354)			
Diabetes mellitus	**0.020**	1.709 (1.086-2.689)			
Hypertension	**0.037**	1.640 (1.030– 2.610)			
Smoking	0.531	0.863 (0.544-1.369)			
Fibrinolytic therapy	0.109	0.693 (0.443-1.085)			
GFR, mL/min	**0.011**	0.988 (0.980-0.997)			
RV-EDD (A4C) (cm)	**<0.001**	3.601 (2.162-5.999)	RV-EDD (A4C) (cm)	**<0.001**	3.227 (1.902-5.474)
RVSP (mmHg)	0.513	1.006 (0.989-1.023)			
LVEF (%)	**<0.001**	0.964 (0.945-0.983)	LVEF (%)	**0.002**	0.968 (0.948-0.988)
WBC, $\times 10^9$/L	**0.001**	1.081 (1.032-1.132)			
Neutrophil, $\times 10^9$/L*	**<0.001***	1.119 (1.057-1.185)			
Lymphocyte, $\times 10^9$/L*	**0.033***	0.722 (0.534-0.975)			
Platelet, $\times 10^9$/L *	**0.028***	1.002 (1.000-1.005)			
SII index >1111	**<0.001**	2.398 (1.457-3.947)	SII index >1111	**0.003**	2.129 (1.290-3.515)

A4C, apical four chamber; GFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; RV-EDD, right ventricular end-diastolic diameter; RVOT, right ventricular outflow tract; RVSP, right ventricular systolic pressure; SII, systemic immune inflammation; WBC, white blood cell. *Neutrophil, lymphocyte and platelet count were not entered to the multivariate model as these parameters are included in the SII index calculation. p<0.05 indicates statistical significance and was shown in bold. characters.

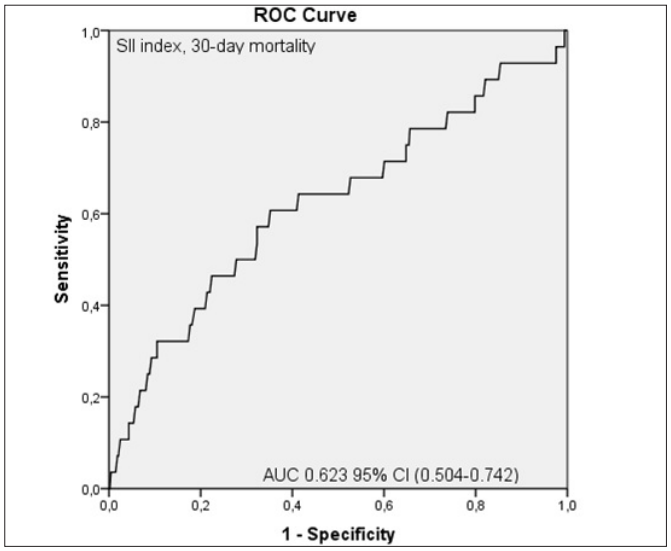

Figure 1a. Receiver operating characteristic (ROC) curves of SII index and 30-day mortality

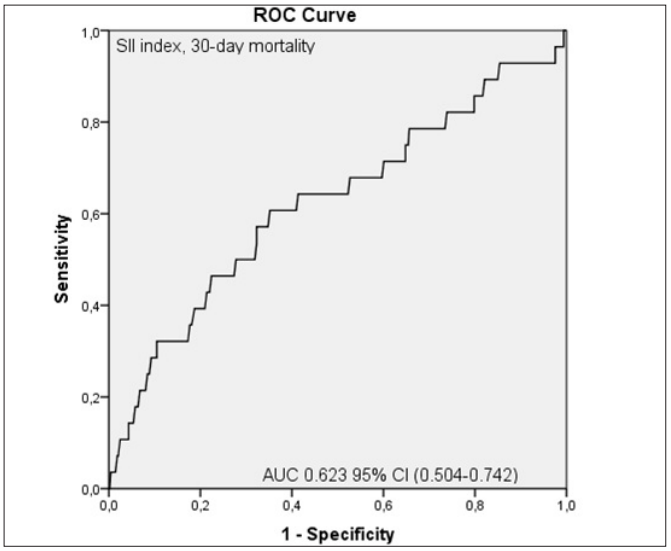

Figure 1b. Receiver operating characteristic (ROC) curves of SII index and long-term mortal**ity**

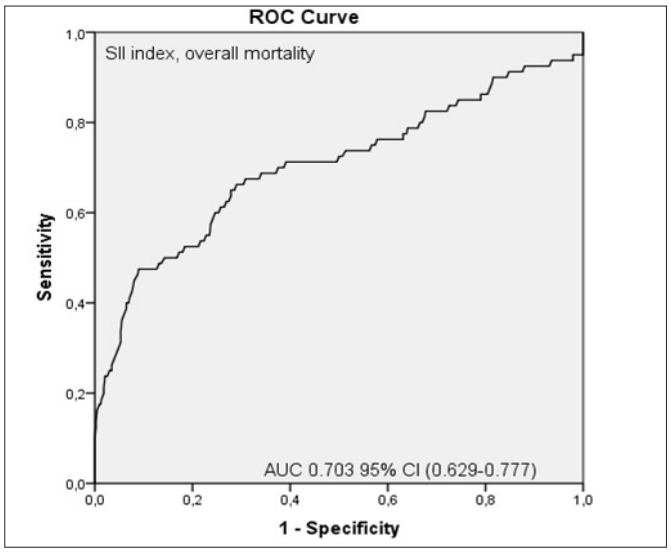

Figure 1c. Receiver operating characteristic (ROC) curves of SII index and overall mortality

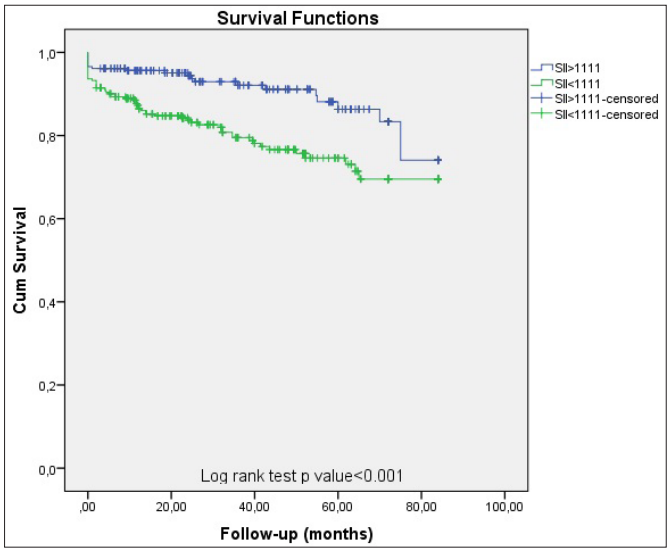

Figure 2. Kaplan-Meier survival curve for overall survival in study population stratified by SII index cut-off values.

DISCUSSION

The main finding of the present study was that a higher SII index boasts good accuracy for predicting all-cause short and long-term mortality in patients with APE. We hypothesized that patients with a higher SII index might experience a more unfavoured prognosis.

An increase in the release of pro-coagulant and pro-inflammatory substances originating from endothelial cells, leukocytes, and platelets was observed in the clinical course of APE (20). Platelet activation and neutrophilic recruitment resulting from the acute inflammatory response were associated with unfavorable prognosis and mortality in APE patients (21). SII is a simple, cheap, and objective index especially studied in patients with malignancy that is thought to reflect the equilibration between the immune and inflammatory responses of the host better than other systemic markers (22). Higher SII generally suggests a reinforced inflammatory and inadequate immune response. It is not known the mechanism for the increased SII index after the onset of APE; however, acute right ventricular overload, circulatory collapse, and increased inflammatory response are thought to be potential causes in the setting of APE.

Many studies are arguing that platelet to lymphocyte ratio and neutrophil to lymphocyte ratio may be short-long term mortality predictors in patients with APE (4-6,23). Neutrophils could play an important role in modulating systemic inflammation and may be used as an indicator of increased inflammatory response. However, in cases of increased apoptosis triggered by stress, together with increased corticosteroid levels, a marked decrease in lymphocyte counts can be observed. In addition, high platelet counts can lead to increased platelet activation and the release of inflammatory mediators, therefore susceptibility to thrombosis occurs (24).

Since the SII index is considered to be an important inflammatory marker, it has been argued that it may be a prognosticator of long-term deaths and adverse events in many cardiovascular diseases. Huang et al. (15) showed that the SII index strongly predicted clinical outcomes, especially in selected elderly patients with acute coronary syndromes. In a study conducted with a large cohort, Yang et al. (16) found that higher SII scores predicted the development of cardiac events after percutaneous coronary intervention. In a recent study, Candemir et al. (17) demonstrated a significant relationship between the severity of coronary artery stenosis calculated using angiographic parameters and the SII index. Furthermore, Gok et al. (18) argued that SII levels were significantly greater in massive APE patients, and this significance progressively increased from nonmassive to massive. However, only in-hospital mortality was evaluated in this study. No studies exist in the literature showing that SII may be a predictor of mortality in long-term follow-up in patients with APE. Thus, we can conclude that this is the initial study to show the long-term prognostic value of the SII index in APE.

We also showed that, in addition to the SII index; age, RV-EDD and LVEF predicted the occurrence of overall mortality entire study population. Age is one of the most important factors affecting the severity of APE and the frequency of adverse events. A significant increase in VTE mortality is observed in elderly patients (25). Conflicting results exist in terms of mortality in patients with RV dysfunction and dilatation on echocardiography (26,27). Since echocardiography is a subjective evaluation, it has been shown that RV diameters and RV/LV ratios measured by computed tomography are determinants in terms of mortality (28). Both the incidence of APE and the frequency of mortality increase significantly in heart failure patients with low LVEF (29,30).

Limitations

Some limitations exist to be considered in our study. First, this was intended as a single-center retrospective cohort study. Second, the SII index was evaluated only at admission; it would be remarkable to assess whether the SII index alters over time and to determine whether the patient's baseline value differences evolve as they suffer the undesirable event. Prospective clinical follow-up trials are needed to generalize these findings to larger patient populations.

CONCLUSION

This study indicates that the baseline SII index revealed significant predictive value for overall mortality on long-term follow-up in patients with APE. This parameter is easy to calculate and cheap; so, it might be used to distinguish high-risk patients with the worst outcomes and to provide a unique point of view in the treatment, assessment, and prognosis of patients with APE.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.04.2021, Decision No: 2021/126).

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 declare that they have no conflicts of interest to disclose.

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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. Martin KA, Molsberry R, Cuttica MJ, et al. Time Trends in Pulmonary Embolism Mortality Rates in the United States, 1999 to 2018. J Am Heart Assoc 2020; 9: e016784.
2. Vazquez-Garza E, Jerjes-Sanchez C, Navarrete A, Joya-Harrison J, Rodriguez D. Venous thromboembolism: thrombosis, inflammation, and immunothrombosis for clinicians. J Thromb Thrombolysis 2017; 44: 377-85.
3. Branchford BR, Carpenter SL. The role of inflammation in venous thromboembolism. Front Pediatr 2018; 6: 142.
4. Wang Q, Ma J, Jiang Z, et al. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute pulmonary embolism: a systematic review and meta-analysis. Int Angiol 2018; 37: 4-11.
5. Karataş MB, İpek G, Onuk T, et al. Assessment of prognostic value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients with pulmonary embolism. Acta Cardiol Sin 2016; 32: 313-20.
6. Phan T, Brailovsky Y, Fareed J, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict all-cause mortality in acute pulmonary embolism. Clin Appl Thromb Hemost 2020; 26: 1076029619900549.
7. Araz O, Yilmazel Ucar E, Yalcin A, et al. Predictive value of serum Hs-CRP levels for outcomes of pulmonary embolism. Clin Respir J 2016; 10: 163-7.
8. Donzé J, Le Gal G, Fine MJ, et al. Prospective validation of the pulmonary embolism severity index. A clinical prognostic model for pulmonary embolism. Thromb Haemost 2008; 100: 943-8.
9. 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.
10. Vedovati MC, Cimini LA, Pierpaoli L, et al. Prognostic value of respiratory index in haemodynamically stable patients with acute pulmonary embolism: The Respiratory Index model study. Eur Heart J Acute Cardiovasc Care 2020; 9: 286-92.

11. Burgos LM, Scatularo CE, Cigalini IM, et al. The addition of echocardiographic parameters to PESI risk score improves mortality prediction in patients with acute pulmonary embolism: PESI-Echo score. Eur Heart J Acute Cardiovasc Care 2020: zuaa007.
12. Lyhne MD, Kabrhel C, Giordano N, et al. The echocardiographic ratio tricuspid annular plane systolic excursion/pulmonary arterial systolic pressure predicts short-term adverse outcomes in acute pulmonary embolism. Eur Heart J Cardiovasc Imaging 2021; 22: 285-94.
13. Kucher N, Rossi E, De Rosa M, et al. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mmHg or higher. Arch Intern Med 2005; 165: 1777-81.
14. 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.
15. Huang J, Zhang Q, Wang R, et al. Systemic immune-inflammatory index predicts clinical outcomes for elderly patients with acute myocardial infarction receiving percutaneous coronary intervention. Med Sci Monit 2019; 25: 9690-701.
16. 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.
17. Candemir M, Kiziltunç E, Nurkoç S, et al. Relationship between systemic immune-inflammation index (SII) and the severity of stable coronary artery disease. Angiology 2021: 3319720987743.
18. 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.
19. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.
20. Galeano-Valle F, Ordieres-Ortega L, Oblitas CM, et al. Inflammatory Biomarkers in the Short-Term Prognosis of Venous Thromboembolism: A Narrative Review. Int J Mol Sci 2021; 22: 2627.
21. Jo JY, Lee MY, Lee JW, Rho BH, Choi WI. Leukocytes and systemic inflammatory response syndrome as prognostic factors in pulmonary embolism patients. BMC Pulm Med 2013; 13: 74.
22. Li C, Tian W, Zhao F, et al. Systemic immune-inflammation index, SII, for prognosis of elderly patients with newly diagnosed tumors. Oncotarget 2018; 9: 35293-9.
23. Duman D, Sonkaya E, Yıldırım E, et al. Association of Inflammatory Markers with Mortality in Patients Hospitalized with Non-massive Pulmonary Embolism. Turk Thorac J 2021; 22: 24-30.
24. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007; 357: 2482-94.
25. Spirk D, Husmann M, Hayoz D, et al. Predictors of in-hospital mortality in elderly patients with acute venous thrombo-embolism: the SWIss Venous ThromboEmbolism Registry (SWIVTER). Eur Heart J 2012; 33: 921-6.
26. Stein PD, Beemath A, Matta F, et al. Enlarged right ventricle without shock in acute pulmonary embolism: prognosis. Am J Med 2008; 121: 34-42.
27. Coutance G, Cauderlier E, Ehtisham J, et al. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care 2011; 15: R103.
28. Quiroz R, Kucher N, Schoepf UJ, et al. Right ventricular enlargement on chest computed tomography: prognostic role in acute pulmonary embolism. Circulation 2004; 109: 2401-4.
29. Dries DL, Rosenberg YD, Waclawiw MA, et al. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials. J Am Coll Cardiol 1997; 29: 1074-80.
30. Slobodan O, Boris D, Bojana S, et al. Predictive value of heart failure with reduced versus preserved ejection fraction for outcome in pulmonary embolism. ESC Heart Fail 2020; 7: 4061–70

Original Article

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Pre-hospital antithrombotic drug use status of died COVID-19 patients

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ABSTRACT

Objectives: In this study, we determine the prehospital antithrombotic drug use rates of patients in COVID-19 mortality to reveal the differences between patients using antithrombotic drugs and those who did not to show whether antithrombotic drugs impact the duration of stay in intensive care.

Material and Method: This retrospective study was conducted with 291 patients admitted to the Sakarya University Training and Research Hospital emergency department between March 13 and December 1, 2020. Patients whose PCR test was positive and who died in our hospital were included in the study.

Results: The median number of days in the intensive care unit of patients using acetylsalicylic acid (7; 3-11) was longer than patients who were not using acetylsalicylic acid (5; 1-10) (p=0.041). Also, the median days in the intensive care unit of patients who were not using any antithrombotic drug (5; 1-10) was shorter than patients who were using an antithrombotic drug (7;3-11) (p=0.032). There was no difference in patients using or not using other antithrombotic drugs (p=0.640) or acetylsalicylic acid and other antithrombotic drugs (p=0.979).

Conclusion: This study shows that the prehospital use of aspirin has a positive effect on survival as it prolongs the length of stay in the intensive care unit. Since it is known that one of the most important causes of death in COVID-19 is hypercoagulopathy and considering the irreversible antiplatelet activity of aspirin and since this activity lasts for up to 10 days, the result seems reasonable.

Keywords: COVID-19, acetylsalicylic acid, prehospital, antithrombotic

INTRODUCTION

Coronavirus disease 2019 (COVID-19), the severe acute respiratory syndrome, is an infectious condition originated by coronavirus 2 (SARS-CoV-2) (1). COVID-19 can affect multiple organ systems, and in particular, its impact on the respiratory tract has led to an increase in morbidity and mortality worldwide (1). While mortality in COVID-19 is primarily attributed to hypoxemia due to acute respiratory distress syndrome (ARDS) (2), hypercoagulopathy is also defined among the causes in recent studies (3,4).

Thrombotic complications are common in COVID-19 patients (2). Available data on thrombotic complications in COVID-19 cases intimate that the rates of venous thromboembolic situations can occur as leading as 25% to 30%, especially in critically ill inmates and mechanically ventilated cases (3,4). Platelets have an essential function in the pathogenesis of sepsis and thrombosis and are a potential target to limit complications (5).

The most commonly applied parenteral anticoagulants are low molecular weight heparins (LMWH) and unfractionated heparin (6). Furthermore, they have antithrombotic activities, are inferred to have anti-inflammatory and antiviral features (7). Heparin therapy is shown to reduce the binding of the SARS-CoV-2 spike protein to heparan sulfate proteoglycan on the cell surface, thus inhibiting initial infection (8).

Previous studies designate that aspirin is beneficial in preventing ARDS and reducing severe lung damage in animals and human observational researches (9,10). Aspirin is reported to reduce mortality in prehospital use and intensive care use (9). The anti-thrombus effect of aspirin lasts up to 10 days after the last use (11).

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In this study, we determine the prehospital antithrombotic drug use rates of patients in COVID-19 mortality to reveal the differences between patients using antithrombotic drugs and those who did not and to show whether antithrombotic drugs impact the duration of stay in intensive care.

MATERIAL AND METHOD

This retrospective study was conducted with 291 patients admitted to the Sakarya University Training and Research Hospital emergency department between March 13 and December 1, 2020. The patients were diagnosed with PCR-confirmed COVID-19, were hospitalized, and subsequently died. Study protocol Sakarya University Faculty of Medicine Local Ethics Committee (Date: 28.12.2020, Decision No: 71522473/050.01.04/644).

Patients and Study Plan

The necessary data for this retrospective research were collected from the patients' electronic medical documents in the hospital's information system. Patients whose PCR test was positive and who died in our hospital were included in the study. Within the scope of the study, patients' demographic features, length of stay in the hospital, RT-PCR test results, antithrombotic drugs used before hospital admission, and mortality states were recorded.

According to the Ministry of Health Guide, intensive care specialists decided to admit the cases to the intensive care unit (12).

Inclusion and exclusion criteria for the study are as follows:

- **Inclusion criteria:** 18 years and over patients who died with a positive RT-PCR test.
- **Exclusion criteria:** Younger than 18 years patients and whose records could not be reached.

Statistical Analysis

To summarize data from the study, descriptive statistics were given as the mean±standard deviation or median, first quartile, and third quartile according to the distribution of the data. Categorical variables were summarized as number and frequency. The normal distribution of numerical variables was evaluated by histogram, q-q graphs, the Kolmogorov-Smirnov test, and the homogeneity of variance controlled with the Levene test. Independent Samples t-test was used to compare mean age values according to sex, and the Mann-Whitney U test was used to compare median intensive care unit stay according to sex. One-Way ANOVA was used to compare mean ages according to drug type being used, and the Kruskal-Wallis test was used to compare median intensive care unit stay according to drug type being used. Spearman's Rho correlation coefficient was used to evaluate the relationship between age and the duration of intensive care unit stay. The statistical analyses were performed using "Jamovi project (2020), Jamovi (Version 1.6.8) [Computer Software] (Retrieved from https://www.jamovi.org) and JASP (Version 0.14) (Retrieved from https://jasp-stats.org) software and the significance value was $p < 0.05$.

RESULTS

Between 15.03.2020-31.12.2020, 291 patients died due to COVID-19. Among them, 190 (65.3%) were males, and 101 (34.7%) were females. Their mean age was 72.2±12.0. The median intensive care unit stay was 6.0 days. Among the patients, 83 (28.5%) were using acetylsalicylic acid, 12 (4.1%) were using acetylsalicylic acid and other antithrombotic drugs, 36 (12.4%) were using other antithrombotic drugs, and 160 (55.0%) were not using any antithrombotic drug (**Table 1**).

Table 1. Sex, age, and antithrombotic drug use of patients died due to COVID-19

	Overall
Gender (%)	
Male	190 (65.3)
Female	101 (34.7)
Age	72.2±12.0
Days in intensive care unit (median [IQR])	6.0 [2.0-11.0]
Acetylsalicylic acid (%)	
Yes	95 (32.6)
No	196 (67.4)
Drug type (%)	
Acetylsalicylic acid	83 (28.5)
No antithrombotic drug	160 (55.0)
Other antithrombotic drugs	36 (12.4)
Acetylsalicylic acid and other antithrombotic drugs	12 (4.1)
Use of any antithrombotic drugs (%)	
Yes	131 (45.0)
No	160 (55.0)

IQR: Interquartile range

Although the mean age of females (74.1±14.0) was higher than males (71.2±10.7), the difference was not statistically significant (p=0.075). The median duration of intensive care unit stay was not different according to sex (p=0.825) (**Table 2**).

Table 2. Comparison of age and days in intensive care unit according to sex

	Sex		p value
	Male (n=190)	Female (n=101)	
Age	71.2±10.7	74.1±14.0	0.075*
Days in intensive care unit (median [IQR])	7.0 [2.0-11.0]	6.0 [2.0-11.0]	0.825†

* Independent Samples t-test, †Mann Whitney U test, IQR: Interquartile range

The patients were classified into four groups according to the used antithrombotic drug as acetylsalicylic acid, other antithrombotic drugs, acetylsalicylic acid, and other antithrombotic drugs, and no antithrombotic drug groups. No significant difference could be detected among these groups according to age and days in the intensive care unit (p=0.376, p=0.155; respectively) (**Figure 1** and **Table 3**).

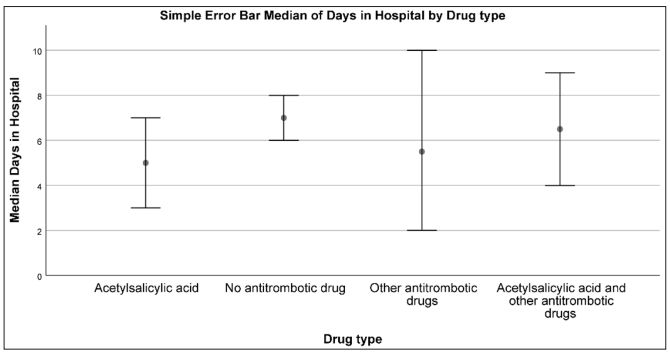

Figure 1. Median days in hospital according to the used antithrombotic drug

Table 3. Comparison of age and days in intensive care unit according to the used antithrombotic drug group

	Age	p value	Days in intensive care unit	p value
Drug type		0.376*		0.155†
Acetylsalicylic acid	71.9±9.82		5 [1-10]	
No antithrombotic drug	71.68±13.67		7 [3-11]	
Other antithrombotic drugs	75.53±8.7		5.5 [2-10.5]	
Acetylsalicylic acid and other antithrombotic drugs	72.17±10.17		6.5 [4.5-8.5]	

*One-Way ANOVA, †Kruskal Wallis

The median number of days in the intensive care unit of patients using acetylsalicylic acid (7; 3-11) was longer than patients who were not using acetylsalicylic acid (5; 1-10) (p=0.041). Also, the median days in the intensive care unit of patients who were not using any antithrombotic drug (5; 1-10) was shorter than patients who were using an antithrombotic drug (7;3-11) (p=0.032). There was no difference in patients using or not using other antithrombotic drugs (p=0.640) or acetylsalicylic acid and other antithrombotic drugs (p=0.979) (**Table 4**).

Table 4. The evaluation of the effect of each drug group on days in the intensive care unit

		Days in intensive care unit	p value*
Acetylsalicylic acid (median [IQR])	No	7 [3-11]	0.041
	Yes	5 [1-10]	
No antitrombotic drug (median [IQR])	No	5 [1-10]	0.032
	Yes	7 [3-11]	
Other antitrombotic drugs (median [IQR])	No	6 [2-11]	0.640
	Yes	5.5 [2-10.5]	
Acetylsalicylic acid and other antithrombotic drugs (median [IQR])	No	6 [2-11]	0.979
	Yes	6.5 [4.5-8.5]	

*Mann Whitney U test

The correlation between age and days in the intensive care unit was not statistically significant (r=-0.049; p=0.407).

DISCUSSION

Hypercoagulation occurs due to excessive thrombin formation and inability to perform fibrinolysis due to endothelial dysfunction due to COVID-19 infection (13). At the same time, hypoxia that occurs in severe COVID-19 can induce thrombosis by increasing blood viscosity and signaling a hypoxia-inducible transcription factor (14). In severe cases, the autopsy conducted on individuals who did not survive revealed that most had microthrombi in pulmonary circulation (15,16). The use of prophylactic antithrombotic drugs is widely recommended in patients diagnosed with COVID-19 (17); however, there are a limited number of studies on prehospital antithrombotic use and effects in COVID-19 patients.

The exact mechanism of sex differences in COVID-19 has not been revealed, but literature indicates the possible mechanisms and the high incidence and deaths in men (18). Studies show that women are more resistant and less susceptible to viral infections than men (19,20). Estrogen has also been reported to increase the activity and proliferation of T cells (19). Similar to the literature, male patients (65.3%) were the majority in our study.

COVID-19 has been reported in all age groups but more severe in elderly patients (21,22). With advanced age, the production of defense cells T and B decreases, which prevents a proper immune response in the presence of infection, with an irregular immune response causing a cytokine storm (23). In addition, it is believed that subclinical inflammation, also called inflammaging in the elderly, contributes to poor prognosis (24). In our study, mortality was higher in the elderly population, and the average age of patients was 72.

COVID-19 pneumonia has significantly amplified the burden on intensive care units. Due to the rising number of cases since the beginning of the pandemic, the number of intensive care beds in xxx increased rapidly. In our study, the time from admission to the intensive care unit until death was determined six days. In a similar study, this period was reported as 12.5 days (25). The late-arriving of patients to intensive care due to occupancy in intensive care units or the differences in intensive care hospitalization indications can cause differences.

Thrombosis prophylaxis plays a vital role in preventing mortality and morbidity due to the hypercoagulation seen in COVID-19 infection (26). In a study of 412 COVID-19 cases, aspirin treatment was correlated with lower mechanical ventilation needs, ICU admission, and fatality risk (26). Aspirin, an irreversible antiplatelet

agent, has been proved to inhibit platelets produced from megakaryocytes from aggregating, also forming microthrombus (27). Aspirin is considered beneficial in lung injury due to decreased platelet-neutrophil clusters in the lungs, reduced inflammation, and raised lipoxin formation, which repairs pulmonary endothelial cell role (26). In a study comparing the effectiveness of aspirin and placebo in 390 patients diagnosed with ARDS, it was found that prehospital drug use decreased intensive care mortality (9). Our study found that the number of days spent in intensive care increased in COVID-19 patients using aspirin before hospital admission, thus extending their life span. This result suggests that prehospital aspirin use may prevent thrombus formation in the early period compared with post-diagnosis use, considering the incubation period, hospital admission time, and PCR result times at the COVID-19 diagnosis stage.

ARDS is one of the common causes of mortality in COVID-19 cases, but the inclusion of all COVID-19 patients confirmed with an RT-PCR in our study may pose a limitation at this point.

CONCLUSION

This study shows that the prehospital use of aspirin has a positive effect on survival as it prolongs the length of stay in the intensive care unit. Since it is known that one of the most important causes of death in COVID-19 is hypercoagulopathy and considering the irreversible antiplatelet activity of aspirin and since this activity lasts for up to 10 days, the result seems reasonable. Our study also provides data for more comprehensive studies to be carried out later.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Sakarya University Faculty of Medicine Local Ethics Committee (Date: 28.12.2020, Decision No: 71522473/050.01.04/644).

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. Rico-Mesa JS, Rosas D, Ahmadian-Tehrani A, White A, Anderson AS, Chilton R. The tole of anticoagulation in COVID-19-induced hypercoagulability. Curr Cardiol Rep 2020; 22: 53.
2. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 1421-4.
3. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145-7.
4. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020; 46: 1089–98.
5. de Stoppelaar SF, van 't Veer C, van der Poll T. The role of platelets in sepsis. Thromb Haemost 2014; 112: 666–77.
6. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: e24S-e43S.
7. Bikdeli B, Madhavan MV, Gupta A, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. Thromb Haemost 2020; 120: 1004–24.
8. Mycroft-West C, Su D, Elli S, et al. The 2019 coronavirus (SARS-cov-2) surface protein (spike) s1 receptor binding domain undergoes conformational change upon heparin binding. BioRxiv 2020: 2020.2002.2029.971093
9. Boyle AJ, Di Gangi S, Hamid UI, et al. Aspirin therapy in patients with acute respiratory distress syndrome (ARDS) is associated with reduced intensive care unit mortality: a prospective analysis. Crit Care Lond Engl 2015; 19: 109.
10. Wang L, Li H, Gu X, Wang Z, Liu S, Chen L. Effect of antiplatelet therapy on acute respiratory distress syndrome and mortality in critically ill patients: a meta-analysis. PloS One 2016; 11: e0154754.
11. Patrono C. Aspirin as an antiplatelet drug. N Engl J Med 1994; 330: 1287–94.
12. COVID-19 Rehberi. 2020. Available from: https://covid19bilgi.saglik.gov.tr/depo/rehberler /COVID-19_Rehberi.pdf
13. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18: 1094–9.
14. Gupta N, Zhao Y-Y, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res 2019; 181: 77–83.
15. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost JTH 2020; 18: 1517–9.
16. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 20209; 383: 120–8.
17. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; 135: 2033–40.
18. Jin J-M, Bai P, He W, et al. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health 2020; 8: 152.
19. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol 2019; 56: 308–21.
20. Hewagama A, Patel D, Yarlagadda S, Strickland FM, Richardson BC. Stronger inflammatory/cytotoxic T-cell response in women identified by microarray analysis. Genes Immun 2009; 10: 509–16.

21. W-j G, Liang W-h, Zhao Y, et al. Comorbidity and its impact on 1,590 patients with COVID-19 in China: a Nationwide analysis. medRxiv. 2020.
22. Mutlu H, Sert ET, Kokulu K, Saritas A. Anxiety level in pre-hospital emergency medical services personnel during coronavirus disease-2019 pandemic. Eurasian J Emerg Med 2021; 20:43-48.
23. Castle SC. Clinical relevance of age-related immune dysfunction. Clin Infect Dis off Publ Infect Dis Soc Am 2000; 31: 578–85.
24. Quiros-Roldan E, Biasiotto G, Zanella I. Letter to the Editor on 'Bonafè M, Prattichizzo F, Giuliani A, Storci G, Sabbatinelli J, Olivieri F. Inflamm-aging: Why older men are the most susceptible to SARS-CoV-2 complicated outcomes. Cytokine Growth Factor Rev'. Cytokine Growth Factor Rev 2020; 54: 1–2.
25. Sousa GJB, Garces TS, Cestari VRF, Florêncio RS, Moreira TMM, Pereira MLD. Mortality and survival of COVID-19. Epidemiol Infect 2020; 148: e123.
26. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19. Anesth Analg 2020: 1-41.
27. Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. EClinicalMedicine 2020; 24: 100434.

Original Article

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Comparison of short-term results of open and laparoscopic surgery in gastric cancer at a new regional hospital: a single surgeon experience

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ABSTRACT

Aim: To compare the short-term results of open and laparoscopic gastrectomy in gastric cancer surgery.

Material and Method: From 15 May 2018 to 28 June 2021, patients who underwent open and laparoscopic gastrectomy for gastric cancer by a single surgeon between were retrospectively analyzed from a prospectively maintained database. Patients were compared in terms of early intraoperative and postoperative outcomes. Both surgical methods were compared in terms of early intraoperative and postoperative outcomes.

Results: A total of 34 patients (open n=23, laparoscopic n=11) were included in the study. While the mean number of lymph nodes was similar between the groups, more metastatic lymph nodes and more advanced disease were detected in the open group (p=0.007, p=0.002, respectively). According to tumor location, patients who underwent laparoscopic gastrectomy were more distally located (p=0.01). The mean operative time was shorter in the open group (171.5 min and 206 min, p=0.006, respectively), while the estimated blood loss was less in the laparoscopic group (158.2 mL vs 186.7 mL, p=0.003). Four patients (17.4%) in the open group and two patients (18%) in the laparoscopic group had at least Clavien-Dindo grade III complications (p=0.96). Earlier gas output was seen in the laparoscopic group (p=0.002), while other postoperative outcomes were similar between the groups. Mean follow-up time was longer in the open group (13.4 months and 7.6 months, respectively, p=0.004).

Conclusion: Until sufficient experience is reached in laparoscopic gastrectomy, choosing earlier stage and distally located tumors is a safe method with postoperative results similar to open gastrectomy.

Keywords: Gastric cancer, open gastrectomy, laparoscopic gastrectomy, experience

INTRODUCTION

According to GLOBACAN 2020 data, gastric cancer is the fifth most common cancer type with a rate of 5,6% and the third most common cause of cancer-related deaths (7.7%) worldwide. Although its incidence is similar in Turkey, it ranks second after lung cancer (8.5%) in cancer-related deaths (1). The curative treatment of gastric cancer without distant metastasis is surgery. In general, surgical treatment aims to resection without leaving any tumor at the surgical margin and radical resection with related regional lymph node dissection (D2 lymphadenectomy) (with or without neoadjuvant or adjuvant chemoradiotherapy). There are various surgical techniques such as total gastrectomy, distal gastrectomy, proximal gastrectomy depending on the stage of the tumor, location, and patient characteristics (2).

Thanks to minimally invasive techniques, laparoscopic gastrectomy (LG) has been developed as an alternative to traditional open gastrectomy (OG) in recent years (3). Recent studies have shown that laparoscopic gastrectomy

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provides a faster recovery with a lower complication rate and less pain than open gastrectomy. Moreover, it has been reported that it is not inferior to open surgery in terms of short-term and long-term survival (3–9). However, the majority of these studies are of Far East origin.

This study aimed to report the short-term results of patients who underwent gastrectomy for gastric cancer at a new regional hospital. We compared the operative characteristics and short-term oncological and postoperative surgical results of open and laparoscopic gastrectomy patients.

MATERIAL AND METHOD

All procedures applied to the participants in the study were under the 1964 Declaration of Helsinki, and the remedial principles and written informed consent forms were obtained from all patients before surgery. This study was approved by Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 23.06.2021, Decision No: 2021/172).

Patients who underwent curative surgery diagnosed with gastric cancer between 5 August 2018 – 1 June 2021, in the Şehit Prof. Dr. İlhan Varank Training and Research Hospital were included in the study. Patients operated for benign disease, patients operated for malignancies other than adenocarcinoma, and patients who underwent palliative surgery were excluded from the study. Demographic characteristics of the patients and American Society of Anesthesiologists (ASA) scores, the surgical procedure, duration of surgery, length of hospital stay, time of gas-stool passage, oral intake time, complications, early oncological outcomes, recurrence, and mortality were analyzed retrospectively from a prospectively maintained database.

Patient Selection and Evaluation

Upper gastrointestinal system endoscopy was performed in all patients preoperatively, and after the histopathological diagnosis was confirmed, thoracoabdominal and pelvis computed tomography (CT) was performed for clinical staging. Antibiotic prophylaxis (2 g cefazolin i.v.) was administered to all patients preoperatively, and additional doses of antibiotics were administered in cases whose operation time exceeded 4 hours. low-molecular-weight heparin (LMWH) was administered 8 to 10 hours before the operation for venous thromboembolism prophylaxis, and medium pressure anti- embolic stockings were worn on the morning of the operation. All patients were evaluated in routine outpatient clinic control on the 10th day after discharge and after the pathology results were obtained (within approximately three weeks). Subsequent follow-ups were performed every 3-6 months in the first year and, every 6-12 months in the following years, depending on the stage of the disease. Postoperative complications were recorded, and the Clavien-Dindo Classification (10) was used for severity. The histopathological classification was made according to WHO 2010 (11). The staging was evaluated by the American Cancer Committee (AJCC) 8th Edition.

Surgical Technique

All surgeries were performed by the same surgeon (B.G). D2 lymph node dissection was performed routinely in all patients. Open surgery was routinely performed in cases with serosal tumor invasion (T4a), multi-visceral organ resection (T4b), tumor located in the cardia, and a history of the previous laparotomy. The surgeon and the patient made the decision for laparoscopic or open gastrectomy for tumors other than these. The operative time was defined as the time from the first skin incision to the last skin suture. Lymph node dissection was performed according to the Japanese gastric cancer guidelines (12). Roux-en-Y anastomosis (gastrojejunostomy or esophagojejunostomy) was applied in all surgeries for reconstruction, and all anastomoses were performed intracorporeally in laparoscopic surgeries.

Laparoscopic Gastrectomy

Total Gastrectomy: The patient was placed on the table in the supine position with the legs closed. The operation began with the camera at the patient's left shoulder level and the surgeon on the right of the patient. After the pneumoperitoneum was created with a Veress needle from the supraumbilical area, a 30-degree camera trocar (Covidien™) was inserted. The pressure was adjusted to be 10-12 mm/Hg using carbon dioxide gas. The operation started in approximately 30 degrees reverse Trendelenburg position. There were three trocars used one 12 mm from the right midclavicular and umbilicus level, one 5 mm from the right subcostal area, and one 5 mm from the left midclavicular-umbilicus level, excluding the left camera port (**Figure 1**). Two straight needles were tied together with No. 1 silk for liver resection, and gauze was inserted between the needles and placed under the liver. Both needles were removed from the right and left sides of the xiphoid, and the liver was lifted by hanging. The area between the omentum majus and the transverse mesocolon was dissected, and the left gastroepiploic vessels and gastrica breves were ligated together with the regional lymph nodes (no 4) and cut. Then, the right gastroepiploic vessels were cut using a laparoscopic clip (Weck® Hem-O-Lok® Polymer Ligation, Teleflex Medical, Morrisville, USA) at the level of the head of the pancreas with regional lymph nodes (no 6). After dissecting the supra-pyloric region (no 5) and mobilizing the stomach, the duodenum was divided 2 cm below the pylorus with a linear

stapler (Endo GIA™ Articulous Reload with Tri-Staple™ Technology, Covidien™, USA) (**Figure 2A**). After the right gastric artery and vein were ligated and cut, the lymph nodes around the hepatoduodenal ligament (no 8) were cleaned. After the celiac artery (no 9) and lymph nodes above the splenic artery (no 11) were dissected, the left gastric artery and vein (no 7) were cut with a similar clip. Right (no 1) and left (no 2) paracardial lymph nodes were dissected, and the esophagus was freed, and then proximal resection was performed with a linear stapler (**Figure 2B**), and It was removed from the Phinnelstein incision using a wound protector (Alexis® Wound Protector/Retractor, Rancho Santa Margarita, USA). After obtaining the pneumoperitoneum, the reconstruction phase was initiated. The ligament of Trietz was divided approximately 40 cm distal and a Roux-en-Y esophagojejunostomy anastomosis was performed with a circular stapler (EEA 25, Covidien®, USA) or linear stapler (**Figure 2C-D**). The jejunum stump was closed with a linear stapler (**Figure 2E**). A side-to-side isoperistaltic jejunojejunostomy anastomosis 50 cm distal to the anastomosis was performed with a linear stapler, and the stapler opening was closed with a linear stapler again (**Figure 2G-F**).

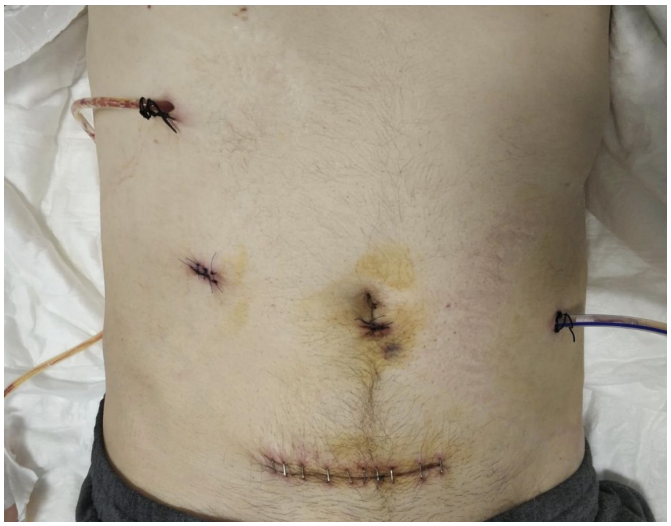

Figure 1. Postoperative trocar sites and Phinnelstein incision

Distal Gastrectomy

After all procedures were performed as described in total gastrectomy, except the preservation of the gastrica breves (no 4sa), the left paracardial area (no 2) and the distal splenic artery (11d); the stomach was resected approximately 5 cm proximal to the tumor using a linear stapler. Gastrojejunostomy anastomosis was performed with a linear stapler from the posterior of the stapler line to the greater curvature. The anastomotic opening was closed with a laparoscopic suture (V-Loc™, Medtronic™) or a linear stapler. Jejunojejunostomy anastomosis was performed as described above.

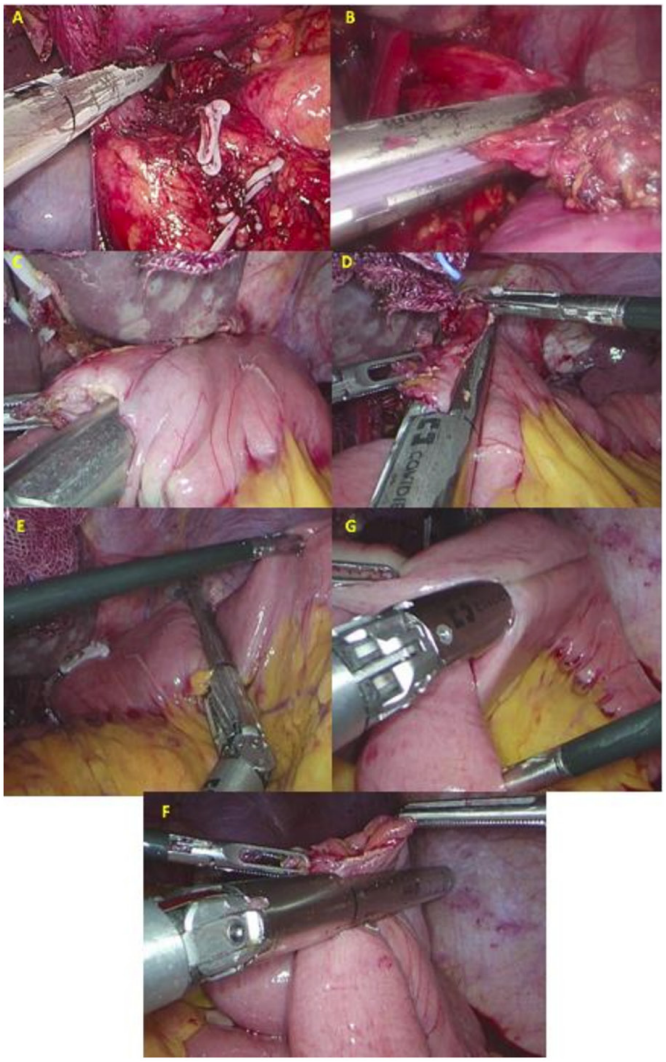

Figure 2. Laparoscopic total gastrectomy stages. **A:** Transection of the duodenum, **B:** Transection of the esophagus, **C:** Esophagojejunostomy anastomosis with linear stapler, **D:** Closing the staple opening after esophagojejunostomy anastomosis with a similar linear stapler, **E:** Transection of the jejunum, **G:** Jejunojejunostomy anastomosis with linear stapler, **F:** Closing the staple opening after jejunojejunostomy anastomosis with a similar linear stapler

Open gastrectomy

A laparotomy was performed with a midline incision. Total gastrectomy and distal gastrectomy were performed as described in the laparoscopic procedure.

Proximal Gastrectomy

Except for the preservation of the right gastropepiploic vessels, right gastric vessels, peripyloric region (no 5, 6), around the hepatoduodenal ligament (no 12) and distal splenic artery (11d), other lymph node stations were excised as described in total gastrectomy. Proximal resection was performed by dividing the esophagus with a linear stapler. Then, the stomach was divided with a linear stapler so that the antrum and pylorus were preserved distally, and the distal resection was completed. The esophagogastric anastomosis was performed with a circular stapler (EEA 25, Covidien®, USA).

Statistical Analysis

Descriptive statistics were calculated as frequencies and percentages for all variables. Normally distributed continuous variables were presented as mean±standard deviation (SD). Categorical data were analyzed using the chi-square test. The Mann-Whitney U test was used for intergroup comparisons of non-normally distributed parameters, and Student's-t independent test was used for intergroup comparisons of normally distributed parameters. The significance level was determined as $p < 0.05$. SPSS for Windows (20.0, SPSS, Chicago, United States of America) was used for all analyses.

RESULTS

A total of 42 patients underwent gastrectomy. Four patients (neuroendocrine tumor n=2, gastrointestinal stromal tumor n=2) due to non-adenocarcinoma pathologies, three patients (peptic ulcer bleeding n=2, pyloric stenosis n=1) due to benign disease, and one patient who underwent palliative surgery were excluded. Then, the remaining 34 patients (male n=25, female n=9) were included in the study. The mean age was 62.2±10.5, and the median follow-up was ten months (2-28 months). The most common tumor localization was the corpus (35.2%), followed by cardia (26.4%) and incisura angularis (17.6%). The mean operative time was 182.7±28 minutes, the estimated blood loss (EBL) was 177.5±29 mL, and the median hospital stay was five days (4-45 days). In laparoscopic gastrectomy, no conversion to open surgery occurred in any patient.

Comparison of Open and Laparoscopic Gastrectomy Results

Open gastrectomy (total n=18, distal=3, proximal n=2) was performed in 23 patients, and laparoscopic gastrectomy (total n=5, distal n=6) was performed in 11 patients. Demographic data were similar between the two groups. When evaluated according to tumor location, the open gastrectomy group (18 patients, 78%) was mostly located proximal-middle (most common corpus, second cardia), while the laparoscopic gastrectomy group was mostly (8 patients, 73%) distal located (most common antrum, second incisura angularis) (p=0.01). While total gastrectomy was performed in 18 (78%) patients in the open group, distal gastrectomy was performed in 6 (54.5%) and total gastrectomy in 5 (45.5%) patients in the laparoscopic group. Additional organ resection was performed in five patients (22%) in the open group and two (18%) in the laparoscopic group. While the mean operative time was shorter in the open group than in the laparoscopic group (171.5 min and 206 min, respectively, p=0.006), the EBLwas less in the laparoscopic group (158.2 mL vs 186.7 mL, p=0.003) (**Table 1**).

Table 1. Comparison of demographic and intraoperative characteristics

	Open (n=23)	Laparoscopic (n=11)	p
Age	63±12	62±8	0.782
Sex, n %			0.665
Female	6 (26)	3 (27)	
Male	17 (74)	8 (73)	
BMI (kg/m²)	26.7±3.4	25.4±2.2	0.183
ASA, n %			0.441
I	5 (22)	2 (18)	
II	6 (26)	6 (54)	
III	12 (52)	3 (28)	0.441
Tumor location, n %			0.01
Cardia	8 (34.8)	1 (9.1)	
Corpus	10 (43.5)	2 (18.1)	
Lesser curvature	1 (4.3)	0	
Incissura angularis	1 (4.3)	5 (45.5)	
Antrum	2 (8.7)	3 (27.2)	
Other	1 (4.3)	0	
Surgical procedure, n %			0.283
Total	18 (78.2)	5 (45.5)	
Distal	3 (13.1)	6 (54.5)	
Proximal	2 (8.7)	0	
Additional organ resection, n %			0.668
Gall bladder	1 (4.4)	1 (9)	
Transvers colon	2 (8.7)	0	
Sigmoid colon	1 (4.4)	1 (9)	
Liver	1 (4.4)	0	
Operative time (min)	171.5±17.3	206.4±32.6	0.006
Estimated blood loss (mL)	186.7±28.7	158.2±20.4	0.003

BMI: body mass index, ASA: American Society of Anesthesiologists

The histopathological features, mean tumor size and the number of lymph nodes removed were similar between the groups. More metastatic lymph nodes were detected in the open group (9.3 vs. 1.7, p=0.007). According to TNM Stage, the more advanced disease was detected in the open group (p=0.002). The majority of patients in the open group (65%) were Stage 3 ≥, the majority of the patients in the laparoscopic group (73%) were Stage 2 ≤ (**Table 2**).

Clavien-Dindo grade ≥ III complications were seen in four (17.4%) patients in the open group and two (18%) patients in the laparoscopic group, with a total of six patients (17.6%) (p=0.96). There was an earlier gas passage in the laparoscopic group with a mean difference of one day (p=0.002). Peritoneal recurrence was detected in two patients (5.8%) during their follow-up, while these two patients were in the open group. No operative or disease-related mortality was observed. One patient in the laparoscopic group died due to suicide at the 2nd month postoperatively, and one in the open group died due to COVID-19 at the 15th postoperative month. The mean follow-up period was longer in the open group than in the laparoscopic group (13.4 months and 7.6 months, respectively, p=0.004) (**Table 3**).

Table 2. Comparison of histopathological and oncological results

	Open (n=23)	Laparoscopic (n=11)	p
Histopathology			0.232
Tubuler adenocarcinoma	15	8	
Mixt type adenocarcinoma	5	1	
Mucinous adenocarcinoma	2	1	
Signet ring cell adenocarcinoma	1	1	
Tumor size (mm)	45.9±18.4	43.25±18.4	0.665
Number of harvested lymph node	41.5±14.1	37.6±8.3	0.326
Number of metastatic lymph node	9.3±11.9	1.7±2.8	0.007
Positive surgical margin	0	0	-
pT stage. n %			0.054
1A	1 (4.4)	1 (9)	
1B	0	0	
2	2 (8.7)	4 (36.4)	
3	15 (65)	6 (54.5)	
4A	4 (17.4)	0	
4B	1 (4.4)	0	
pN stage. n %			0.009
0	4 (17.4)	6 (54.5)	
1	3 (13)	2 (18.2)	
2	5 (21.7)	2 (18.2)	
3A	8 (34.8)	1 (9)	
3B	3 (13)	0	
pTNM stage. n %			0.002
1A	1 (4.4)	2 (18.2)	
1B	0	2 (18.2)	
2A	1 (4.4)	3 (27.2)	
2B	6 (26)	1 (9)	
3A	4 (17.4)	2 (18.2)	
3B	8 (34.8)	1 (9)	
3C	3 (13)	0	

Table 3. Comparison of the groups in terms of postoperative complications and follow-up

	Open (n=23)	Laparoscopic (n=11)	p
Clavien-Dindo, n %			0.96
IIIA	2 (8.7)	1 (9)	
Esophagojejunostomy anastomotic leak	2	1	
≥IIIB	2 (8.7)	1 (9)	
Duodenal stump leak	1	0	
Bleeding	1	0	
Stapler line opening	0	1	
Gas output (day)	2.4±0.8	1.5±0.5	0.002
Stool output (day)	2.6±0.7	2.5±0.8	0.821
Oral intake time (day)	1.6±0.9	1.2±0.4	0.095
Lenght of hospital stay (DAY)	7.7±8.6	8.4±8.4	0.842
Readmission, n %	2 (8.7)	1 (9)	0.97
Reoperation, n %	2 (8.7)	1 (9)	0.97
Recurrence, n %	2 (8.7)	0 (0)	0.162
Mortality, n %	1 (4.4)	1 (9)	0.645
Follow up (month)	13.4±7.8 10 (2-28)	7.6±3.1 9 (2-12)	0.004

DISCUSSION

Laparoscopic gastrectomy provides an advantage with less blood loss in patients undergoing curative surgery with D2 lymph node dissection in gastric cancer. In contrast, open gastrectomy stands out with a shorter operation time. Both methods were similar in terms of the number of harvested lymph nodes and postoperative outcomes such as serious complications, length of hospital stay, and need for reoperation.

Many studies have shown that laparoscopic gastrectomy has advantages over open surgery in terms of early results. These include less complication rate, shorter hospital stay, earlier gas passage, less blood loss, and less postoperative pain. On the other hand, longer operative times were found in laparoscopic gastrectomy (4,5,13–16). In a multicenter randomized controlled trial (RCT) (KLASS-01) conducted with a total of 1416 patients (laparoscopic n=705, open n=711) in 2016, it was reported that laparoscopic surgery was advantageous over open surgery in terms of early postoperative results (particularly wound infection) in patients with stage 1 gastric cancer (4). In the long-term results of the same study reported in 2019, similar overall and cancer-specific survival rates were reported, and it was shown to be safe in terms of oncology (3). Another RCT (KLASS-02) with locally advanced gastric cancers showed similar three-year recurrence-free survival rates between laparoscopic and open gastrectomy (laparoscopic 80.3%, open 81.3%) (5). Our study had earlier gas passage and less blood loss in the laparoscopic group, similar to the literature. The majority of the open group (78%) and half of the laparoscopic group (54.5%) were total gastrectomies. However, the mean operative time was longer in the laparoscopic group (171.5 min versus 206 min). Bleeding in laparoscopic surgeries causes dissection plans to disappear, and complications increase. Therefore, at the beginning of the technique, the surgeon aimed to perform a more careful dissection for safe surgery. In addition, the added effort to adhere to oncological principles has been the main reason for the longer operative time in laparoscopic gastrectomy. The lack of conversion to open surgery is the result of this attention.

The laparoscopic group included tumors located more distally. There were two technical and oncological reasons for this. The first was because the surgeon initially selected distally located tumors because it was relatively easier for laparoscopic gastrectomy (17,18). The second was due to concerns about surgical margin safety in proximal tumors. Similarly, patients in the laparoscopic group had an earlier stage. Although RCTs reported that laparoscopic gastrectomy is not inferior to open gastrectomy in terms of both early and long-term

results in locally advanced gastric cancer, these studies are the results of experienced centers (5,7). Concern for oncologic outcomes led the surgeon to initially select early-stage tumors.

There was no difference between the groups regarding postoperative complications (Clavien-Dindo Grade ≥III) and reoperation rates. In the open gastrectomy (distal gastrectomy) group, a patient who used anticoagulants for cardiac valve replacement was re-operated on the first postoperative day due to bleeding. Hemostasis was performed upon detection of bleeding in the form of leakage around the splenic hilus, and the patient was discharged on the eighth postoperative day without any problem. Another patient, on the fifth day after discharge (postoperative day 10), was operated again due to the detection of contrast leakage in the oral contrast CT performed with the complaint of fever and abdominal pain. More than 50% separation was detected in the gastrojejunostomy staple line and it was converted to total gastrectomy. In this patient and other distal gastrectomy surgeries, the gastrojejunostomy anastomosis was performed (manually or with a stapler) from the posterior of the staple line to the greater curvature, after the proximal stomach was divided with a linear stapler. In this patient, separation was not in the gastrojejunostomy anastomosis but anterior to this anastomosis, in the section divided by the linear stapler. Reinforcement sutures were not routinely placed on the staple line in any case. Therefore, the current situation is likely to have occurred due to a problem with the stapler used. In the laparoscopic gastrectomy group, one patient was reoperated for duodenal stump leakage. This patient underwent simultaneous laparoscopic distal gastrectomy and anterior resection for synchronous gastric and sigmoid colon cancer (19). Esophagojejunostomy anastomotic leakage was detected in three patients (laparoscopic n=1, open n=2) and all were treated conservatively.

In gastric cancer, whose curative treatment is surgical, R0 resection and adequate lymph node dissection are the most critical parameters that increase the postoperative survival time. In a meta-analysis evaluating the effect of D1 and D2 lymph node dissection on gastric cancer survival, it was reported that there was no difference in survival in early-stage (T1-2) patients, but D2 dissection had significant survival benefit compared to D1 dissection in higher stage (T3-4) patients (13.5% for D1 and 19.5% for D2) (20). In our study, an early-stage tumor (T1-2, N0) could not be diagnosed or determined in any patient with preoperative staging. Therefore, standard D2 lymph node dissection was performed in all patients. In the pathological staging results, early-stage tumors were detected in a total of five (14.7%) patients (laparoscopic 80%, open 20%).

At least 15 lymph node dissections are required for the reliable staging of gastric cancer (21). In our study, adequate lymph node dissection was performed in all patients (minimum 20 – maximum 75, **Table 2**). In addition, the mean number of lymph nodes dissected was similar in both groups (open 41.5, laparoscopic 37.6, p=0.32). Both the absence of positive surgical margins and adequate lymphadenectomy are indicators of the oncological reliability of this study. Two patients with total recurrence were also in the open gastrectomy group. The main reason for this situation is that patients who underwent open gastrectomy have more advanced disease and more extended follow-up periods.

Limitations and Strenghts of the Study

This study has some limitations. First of all, this is a retrospective study conducted in a single center. Second, there are relatively few cases. Third, the decision for laparoscopic or open gastrectomy was made primarily by the surgeon, and earlier stage tumors were selected. This causes selection bias. Finally, we did not use endoscopic ultrasonography (EUS) for preoperative staging. The main reason for this is the absence of an EUS device and an experienced healthcare professional. On the other hand, the completeness of the data and the absence of loss in follow-up are the strengths of the study.

CONCLUSION

In this study, the experiences of a single surgeon who performed gastrectomy for gastric cancer at a new regional hospital were presented. The short-term results of patients who underwent laparoscopic and open gastrectomy were compared. Especially in laparoscopic gastrectomy, until sufficient experience is reached, choosing earlier stage and distally located tumors may be a safe option with postoperative results similar to open gastrectomy.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 23.06.2021, Decision No: 2021 / 172).

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. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-49.
2. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. The Lancet. 2020; 396: 635–48.
3. Kim HH, Han SU, Kim MC, et al. Effect of laparoscopic distal gastrectomy vs open distal gastrectomy on long-term survival among patients with stage I gastric cancer: the KLASS-01 randomized clinical trial. JAMA Oncol 2019; 5: 506-13.
4. Kim W, Kim HH, Han SU, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage ı gastric cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS-01). Ann Surg 2016; 263: 28–35.
5. Hyung WJ, Yang HK, Park YK, et al. Long-term outcomes of laparoscopic distal gastrectomy for locally advanced gastric cancer: the KLASS-02-RCT randomized clinical trial. JCO 2020; 38: 3304–13.
6. van der Wielen N, Straatman J, Daams F, et al. Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. Gastric Cancer 2021; 24: 258–71.
7. Lee H-J, Hyung WJ, Yang H-K, et al. Short-term outcomes of a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy with D2 lymphadenectomy to open distal gastrectomy for locally advanced gastric cancer (KLASS-02-RCT). Ann Surg 2019; 270: 983–91.
8. Yu J, Huang C, Sun Y, et al. Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer. JAMA 2019; 321: 1983–92.
9. Liu F, Huang C, Xu Z, et al. Morbidity and mortality of laparoscopic vs open total gastrectomy for clinical stage i gastric cancer: the CLASS02 multicenter randomized clinical trial. JAMA Oncol 2020; 6: 1590-97.
10. Dindo D, Demartines N, Clavien PA. Classification of surgical complications. Ann Surg 2004; 240: 205–13.
11. Berlth F, Bollschweiler E, Drebber U, Hoelscher AH, Moenig S. Pathohistological classification systems in gastric cancer: Diagnostic relevance and prognostic value. World J Gastroenterol 2014; 20: 5679–84.
12. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021; 24: 1–21.
13. Zeng F, Chen L, Liao M, et al. Laparoscopic versus open gastrectomy for gastric cancer. World J Surg Oncol 2020; 18: 20.
14. Zhang W, Huang Z, Zhang J, Che X. Long-term and short-term outcomes after laparoscopic versus open surgery for advanced gastric cancer: An updated meta-analysis. J Minim Access Surg. 2021 May 6. doi: 10.4103/jmas.JMAS_219_20. Epub ahead of print. PMID: 34045399.
15. Ammori BJ, Asmer H, Al-Najjar H, et al. Laparoscopic versus open D2 gastrectomy for gastric cancer: a case-matched comparative study. J Laparoendosc Adv Surg Tech A 2020; 30: 777–82.
16. Li B, Yu-Hong Wong I, Siu-Yin Chan F, et al. Comparison of laparoscopic versus open gastrectomy for gastric cancer. Surg Oncol 2020; 35: 14–21.
17. Jung DH, Son S-Y, Park YS, et al. The learning curve associated with laparoscopic total gastrectomy. Gastric Cancer 2016; 19: 264–72.
18. Chi F, Lan Y, Zhou S, Yang L, Chen M, Bi T. Learning curve of totally laparoscopic distal gastrectomy for gastric cancer: a single teaching hospital study. Wideochir Inne Tech Maloinwazyjne. 2018; 13: 442–7.
19. Goksoy B. Simultaneous totally laparoscopic distal gastrectomy and anterior resection for synchronous gastric and colon cancer. Cureus 2021; 13: e15692.
20. Seevaratnam R, Bocicariu A, Cardoso R, et al. A meta-analysis of D1 versus D2 lymph node dissection. Gastric Cancer 2012; 15: 60–9.
21. Naffouje SA, Salti GI. Extensive lymph node dissection improves survival among american patients with gastric adenocarcinoma treated surgically: analysis of the national cancer database. J Gastric Cancer 2017; 17: 319–30.

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Clinical and epidemiological features of amyotrophic lateral sclerosis in eastern Turkey

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ABSTRACT

Aim: The number of studies on the epidemiological and clinical data of amyotrophic lateral sclerosis (ALS) patients in Turkey is quite low and the studies on this subject reflect the data of western regions of Turkey. In this study, we aimed to present the demographic, clinical and mortality features of ALS patients diagnosed in the last 10 years in a large reference hospital in the Eastern Anatolia region of Turkey.

Material and Method: 42 ALS patients diagnosed between January 2011 and January 2021 in Atatürk University, Faculty of Medicine, Department of Neurology were included in the study. The data of the patients were obtained by retrospectively scanning the patient electronic files registered in the database of our hospital. The age, gender, examination findings, clinical course, treatments they received and the cause of death of the patients were recorded.

Results: 26 of ALS patients were men and 16 were women. The mean age of onset was 53.4±12.3 and the mean diagnostic delay was 13.6±6.9 months. 64.2% of the patients had onset in the spinal region, and 35.7% in the bulbar region. Weakness/atrophy of the upper extremity muscles and swallowing difficulty were the most common onset symptoms. All ALS patients were using riluzole. 11 ALS patients died. The mean time between diagnosis and death in patients who died was 27.2±18.6 months. The most common causes of death in ALS patients were pneumonia and sepsis.

Conclusion: Age of onset of ALS was low in our patients. The number of patients in the clinically definite ALS group was the highest. Weakness/atrophy of the upper extremity muscles and swallowing difficulty were the most common onset symptoms. Approximately 2/3 of the patients had spinal, and 1/3 bulbar region onset. There was no significant difference between spinal and bulbar onset patients in terms of gender, age of disease onset, mortality, and life expectancy of patients with death. The rate of using riluzole was high. The most common causes of death in ALS patients were pneumonia and sepsis.

Keywords: Amyotrophic lateral sclerosis, epidemiology, clinical, eastern, Turkey, mortality

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is a progressive disease that causes muscle weakness as a result of the degeneration of upper and lower motor neurons. Although ALS is a disease described in 1869, its cause and pathogenesis are still largely unknown and there is currently no definitive treatment (1). The incidence of ALS is 0.4-3/100,000 and its prevalence is 3-8/100.000 (2). Clinical findings usually start at the age of 50-60. Approximately 5-10% of all ALS cases are familial and 90-95% are sporadic ALS (3,4).

Clinical findings in patients with ALS consist of lower motor neuron findings such as asymmetric weakness in arm and leg muscles, atrophy, fasciculation, dysphasia, and swallowing difficulty, as well as upper motor neuron findings such as hyperreflexia and spasticity that occur as a result of degeneration of the lateral corticospinal tracts in the spinal cord.

The diagnosis of ALS is made as a result of the patient's history, physical examination findings, and data obtained through electrophysiological tests. Sometimes neuroimaging methods, blood tests, genetic studies and rarely muscle biopsy may be required to exclude other possible diagnoses. Revised El-Escorial diagnostic criteria defined by Brooks et al. in 2000 are used in the diagnosis of ALS (5).

ALS is a chronic, progressive, and mortal disease, and long-term and detailed follow-up of patients with ALS is significant.

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The number of studies on the epidemiological and clinical data of ALS patients in Turkey is quite low and the studies on this subject mostly reflect the data of western regions of Turkey. In our study, we aimed to present the demographic, clinical and mortality features of ALS patients diagnosed in the last 10 years in a large reference hospital in the Eastern Anatolia region of Turkey.

MATERIAL AND METHOD

Ethics committee approval was obtained from Atatürk University Faculty of Medicine, Clinical Research Ethics Committee (Date: 15.04.2021, Decision No: 183). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Forty-two ALS patients diagnosed between January 2011-January 2021 in the Department of Neurology clinic, Faculty of Medicine, Atatürk University were included in the study. The data of the patients were obtained by retrospectively scanning the patient electronic files registered in the database of our hospital. ALS diagnosis was made according to the revised El-Escorial criteria to the patients. Electromyography (nerve conduction studies and needle electromyography) and spinal magnetic resonance imaging were performed in all patients. Conditions included in the differential diagnosis of ALS such as myelopathy, multifocal motor neuropathy, paraneoplastic syndrome, and infection were excluded by appropriate laboratory and imaging methods. Diagnosed ALS patients were followed up clinically at 3-6 month intervals. At each control examination or hospital admission, patients were re-evaluated in terms of revised El-Escorial criteria and electrophysiologically, and the patients' examination findings, clinical course, treatments, gastrostomy, tracheostomy, and cause of death were recorded. Patients who were out of followed up for various reasons over time were not included in the study.

Statistical Analysis

Study data were analysed by using SPSS 22 (Statistical Package for the Social Sciences) program. Data compliance for normal distribution was evaluated with the Kolmogorov Smirnov test. Chi-Square test was used in the analysis of categorical data between the groups, and the Mann Whitney U test was used in the analysis of numerical data that did not comply with normal distribution. Statistical significance level was accepted as p <0,05. Descriptive statistics such as age, gender, onset region, onset symptoms were calculated as mean, standard deviation, range, and percentage.

RESULTS

26 (61.9%) of ALS patients were male, and 16 (38.1%) were female. The male/female rate was in favor of the male gender with 1,62. Mean age of onset was 54±10.7 in male patients; 52.5±14.8 in female patients. The mean diagnostic delay from the onset of symptoms to diagnosis in ALS patients was 13.6±6.9 months. There was no statistically significant difference between male and female patients in terms of mean age of onset and diagnostic delay (p>0.05). Detailed distribution of patients by age and gender is shown in **Table 1**. 64.2% of the patients had onset in the spinal region, and 35.7% in the bulbar region. No statistically significant difference was found between spinal and bulbar-onset patients in terms of gender, age of disease onset, mortality and life expectancy of patients with death (p>0.05)(**Table 2**). Weakness/atrophy of upper extremity muscles and swallowing difficulty were the most common onset symptoms at first admission (**Table 3**). According to the revised El-Escorial criteria, the number of patients in the clinically definite and probable ALS groups was in the majority (**Table 3**). All ALS patients were using riluzole and only 2 patients were receiving speech therapy (**Table 3**). 11 ALS patients died. The mean time between diagnosis and death in patients who died was 27.2±18.6 months. No statistically significant difference was found between male and female patients in terms of the time between diagnosis and death and the average age of the patients who died (p>0.05). The most common causes of death in ALS patients were pneumonia and sepsis (**Table 4**).

Tablo 1. Distribution of ALS patients by age and gender

Characteristics of the patients	Total n (%)	Female n (%)	Male n (%)	p
Number	42 (100)	16 (38.1)	26 (61.9)	-
Age groups				
20-29	2 (4.8)	1 (2.4)	1 (2.4)	-
30-39	5 (11.9)	1 (2.4)	4 (9.5)	-
40-49	8 (19)	5 (11.9)	3 (7.1)	-
50-59	10 (23.8)	3 (7.1)	7 (16.7)	-
60-69	15 (35.7)	4 (9.5)	11 (26.2)	-
70-79	2 (4.8)	2 (4.8)	-	-
Disease duration; (Month, mean±SD; median (min-max))	66.9±45.4; 52 (5-192)	63.6±45.5; 48 (9-121)	68.9±46.1; 58 (5-192)	0.659*
Mean age of disease onset (mean±SD; median (min-max)	53.4±12.3; 54 (27-78)	52.5±14.8; 52.5 (27-78)	54±10.7; 54 (29-68)	0.487*
Diagnostic delay (Month, mean±SD; median (min-max))	13.6±6.9; 12.5 (4-40)	12.7±5.3; 12.5 (4-22)	14.2±7.7; 12.5 (4-40)	0.688*

n:number, *Mann Whitney U

Tablo 2. Features of patients according to onset region

Features of patients	Spinal onset	Bulber onset	p
	27 (64.3)	15 (35.7)	
Gender			
Male; n (%)	16 (59.3)	10 (66.7)	0.636*
Female; n(%)	11 (40.7)	5 (33.3)	
Mean age of onset, years mean±SD; median (min-max)	53.3±12.4; 54 (27-78)	53.7±12.5; 53 (31-76)	0.793**
Disease duration, month mean±SD; median (min-max)	65.8±45.3; 56 (5-192)	68.93±47.2; 48 (9-132)	0.713**
Survival time, month mean±SD; median (min-max)	31±21.9; 33.5 (5-56)	22.8±14.9; 20 (9-48)	0.714**
Mortality; n (%)	6 (%22,2)	5 (33.3)	0.676*
No mortality; n (%)	21 (%77.8)	10 (66.7)	

n:number, *Chi-Square ** Mann Whitney U

DISCUSSION

It is known that male gender is a risk factor for ALS.6 Male / female (M/F) rate in ALS patients varies between 1-3 in many studies (6-11). In studies conducted in Antalya province and Thrace region in Turkey, this rate was found as 1.78 and 2 (8,9). The M/F rate was found to be close to these values with 1.62.

When it is examined at the mean age of onset of ALS, different results are obtained in a wide range of age. The mean age of onset of ALS has been reported as 56 and 60, respectively, in Russia and Greece, Turkey's northern and western neighbors (10,11). The mean age of onset of ALS in Turkey was reported as 56 and 58 in two different studies conducted in the western regions of Turkey (8,9).

Table 3. Distribution of the patients according to onset symptoms, revised El-Escorial Criteria and the treatments that are used

	Total (n:42, %)	Female (n:16, %)	Male (n:26, %)	p
Symptoms				
Weakness/atrophy of the upper extremity muscles	31 (73.8)	13 (81.3)	18(69.2)	0.390*
Weakness/atrophy of the lower extremity muscles	14 (33.3)	4 (25.0)	10 (38.5)	0.369*
Fasciculation	15 (35.7)	4 (25.0)	11 (42.3)	0.256*
Swallowing difficulty	20 (47.6)	7 (43.8)	13 (50.0)	0.694*
Aphasia	15 (35.7)	6 (37.5)	9 (34.6)	0.850*
Other	18 (42.9)	11 (68.8)	7 (26.9)	0.008*
Weigh loss	7 (16.6)	4 (9.5)	3 (7.1)	
Cramp	4 (9.5)	3 (7.1)	1 (2.4)	
Aphonia	4 (9.5)	3 (7.1)	1 (2.4)	
Dementia	3 (7.1)	1 (2.4)	2 (4.7)	
ALS patients according to the revised El Escorial Criteria				
Clinically definite ALS	19 (45.2)	6 (14.3)	13 (30.9)	-
Clinically probable ALS	15 (35.7)	6 (14.3)	9 (21.4)	-
Laboratory-supported probable ALS	6 (14.3)	3 (7.1)	3 (7.1)	
Clinically possible ALS	2 (4.8)	1 (2.4)	1 (2.4)	-
Treatments				
Riluzole	42 (100)	16 (38.1)	26 (61.9)	-
Vitamin (B complex, vitamin C, vitamin E)	16 (38.1)	5 (11.9)	11 (26.2)	-
Physical therapy and rehabilitation	19 (45.2)	8 (19)	11 (26.2)	-
Speech therapy	2 (4.8)	1 (2.4)	1 (2.4)	-
Gastrostomy	10 (23.8)	3 (7.1)	7 (16.6)	-
Tracheotomy	11 (26.2)	5 (11.9)	6 (14.3)	-

n:number, **Chi-Square, ALS: Amyotrophic lateral sclerosis

Table 4. Characteristics of ALS patients who died

ALS Patients	Female (n, %)	Male (n, %)	Total (n, %)	p
Mortality	5 (45.4)	6 (54.6)	11 (100)	0.987*
Age(mean±SD; median (min-max)	52.6±14.5; 55 (31-66)	62.1±5.4; 64 (55-67)	57.8±11.1; 62 (31-67)	0.141**
Time between ALS diagnosis and death (mean±SD;median (min-max)	21.4±15.7; 20 (9-48)	32.1±20.8 34.5 (5-56)	27.2±18.6; 20 (5-56)	0.409**
Spinal onset	3 (27.3)	3 (27.3)	6 (54.5)	
Bulbar onset	2 (18.2)	3 (27.3)	5 (45.5)	
Cause of seath				
Pneumonia	2 (18.1)	4 (36.3)	6 (54.4)	
Sepsis	1 (9.1)	1 (9.1)	2 (18.2)	
Pulmonary embolism	1 (9.1)	-	1 (9.1)	
Coronary failure	-	1 (9.1)	1 (9.1)	
Cerebrovascular Disease	1 (9.1)	-		

*Chi-Square, ** Mann Whitney U, ALS: Amyotrophic lateral sclerosis

In our study, the mean age of onset of ALS patients was found to be 53.4±12.3, and this value showed that the mean age of onset of ALS in our patients was lower when compared to the results of two other studies conducted in Turkey. It is known that 5-10% of all ALS cases are familial and the age of onset is about 10 years earlier in the familial form of ALS (12,13). We think that the higher rate of consanguineous marriage in our region compared to the western regions of Turkey where other studies have been conducted may have played a role in this result. Although genetic screening has not been performed on our patients, the fact that more than 1/3 of our patients are under the age of 50 supports the opinion that the number of patients with familial form is high.

The incidence of ALS increases every decade particularly after the age of 40, peaks at the age of 74 and then reduces.2 The peak incidence of ALS onset is between 60 and 75 years in most studies (14). 40.5% of our ALS patients were between the ages of 60-79 and they confirmed this situation.

ALS is a disease that is diagnosed clinically, and its onset symptoms may require differential diagnosis with many diseases. The lack of sufficient biomarkers specific to the clinically used disease and the need to demonstrate progressive spread of the disease in some cases may lead to delay in the diagnosis of ALS. The mean delay between the onset of ALS symptoms and diagnosis was 13.6±10.9 months. This period is specified between 9-24 months in many studies (8,15-17). Results regarding the distribution of onset symptoms have been reported to be contradictory in different studies. In some studies, the most common initial symptom in ALS patients was reported as upper extremity weakness, while in some studies, on the other hand, it was reported as lower extremity weakness (11,18,19). In a study conducted in England, it was reported that the symptoms in 44% of the motor neuron patients start from the upper extremity, in 37% from the lower extremity, 74% have upper extremity weakness and 60% have lower extremity weakness. In the same study, swallowing difficulty was found in 41% of the patients, and dysphasia was found in 23% (20). Weakness/atrophy of the upper extremity muscles (73.8%) was the most common onset symptom in patients, followed by swallowing difficulty with 47.6% and dysphasia with 35.7%.

When patients are classified according to the El-Escorial criteria, the distribution of patients varies in different studies. In a study conducted in Italy, 45% of the patients were clinically definite, 27% were clinically probable ALS; in another study conducted in Sicily, 20% of the patients were evaluated in the clinically definite and 49.4% in the clinically probable ALS group (21,22). In studies conducted in Turkey, these rates are 60% and 75.6% for clinically definite ALS, and it was determined as 24.8% and 11% for clinically probable ALS (8,9). 45.2% of our patients were in the clinically definite ALS group, and 35.7% were in the clinically probable ALS group. While our rate of patients in the clinically probable ALS group was higher than these studies, our rate of clinically definite ALS was low.

In a study conducted in China, it was found that 32.3% of ALS patients used riluzole, 40.3% used vitamins, and 11.3% used conventional Chinese treatments (23). The rate of use of riluzole in ALS patients was 53.6% in Korea, 60.7% in Taiwan, and 86.3% in Germany (24-26). All of our patients were using riluzole and this rate of use was quite high compared to many countries. ALS treatment is not covered by insurance, or solely clinically definite and probable ALS patients are covered by insurance in some countries, however there is no such limitation in riluzole transportation in our country, which we think this led to this different result. Once more, in a study with a high number of patients, it was stated that 76.1% of ALS patients received motor rehabilitation and 25.2% received speech therapy (27). It was noteworthy that nearly half of our patients did not benefit from physical therapy and rehabilitation facilities, and the number of patients receiving speech therapy was very low.

The life expectancy from the onset of ALS to death varies between 24 and 71 months in various studies (23,28). While this period is generally longer in Asian countries, it appears to be shorter in European countries (28). Life expectancy in ALS varies depending on many factors. While conditions such as male gender, late onset age, short diagnostic delay, bulbar onset, low body mass index, exposure to pesticides, living in rural areas are associated with poor prognosis, factors such as female gender, opening tracheostomy, use of riluzole are associated with better prognosis (23,29-31). The life expectancy from the onset of ALS symptoms to death ranged from 5 to 56 months, however the average was 27 months. This period was similar to European countries. No statistically significant difference was found between gender and onset region and life expectancy. The low number of patients who died may have played a role in this different result.

In a post-mortem study conducted by Corcia et al.(32) on ALS patients, they found that the most common causes of death in ALS patients were bronchopneumonia (55%) and aspiration pneumonia (16%). In our study, the most common causes of death in ALS patients were determined as pneumonia and sepsis, and it was consistent with the results of this study.

CONCLUSION

The low age of onset of ALS in our patients and the fact that 35.7% of the patients are under the age of 50 support the opinion that the familial form of ALS may be more in our region. The number of patients in the clinically definite ALS group according to the El-Escorial criteria was the highest. Weakness/atrophy of the upper extremity muscles was the most common onset symptom in our patients, followed by difficulty in swallowing and dysphasia. Approximately 2/3 of the patients had spinal, and 1/3 bulbar region onset. There was no significant difference between spinal and bulbar onset patients in terms of gender, age of disease onset, mortality, and life expectancy of patients with death. The number of patients using Riluzole is high; the number of patients who received physical therapy and speech therapy was low. The most common cause of death in ALS patients were identified as pneumonia and sepsis. This study has some limitations, including the small number of patients and the lack of genetic testing for ALS patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from the Atatürk University, Faculty of Medicine, Clinical Research Ethics Committee (Date: 15.04.2021, Decision No: 183).

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. Charcot JMJ. A. Deux cas d'atrophie musculaire progressive avec lesions de la substance grise et des faisceaux antero-lateraux de la moelle epiniere [French]. Arch Physiol Neurol Pathol 1869; 2: 744.
2. Worms PM. The epidemiology of motor neuron diseases: a review of recent studies. J Neurol Sci 2001; 191: 3.
3. Byrne S, Walsh C, Lynch C, et al. Rate of familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2011; 82: 623-7.
4. Taylor JP, Brown RH Jr, Cleveland DW. Decoding ALS: from genes to mechanism. Nature 2016; 539: 197.
5. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis and other motor neuron disorders: official publication of the World Federation of Neurology, Research Group on Motor Neuron Diseases 2000; 1: 293-9.
6. Manjaly ZR, Scott KM, Abhinav K, et al. The sex ratio in amyotrophic lateral sclerosis: A population based study. Amyotroph Lateral Scler 2010; 11: 439-42.
7. Luna J, Diagana M, Ait Aissa L, et al. Clinical features and prognosis of amyotrophic lateral sclerosis in Africa: the TROPALS study. J Neurol Neurosurg Psychiatry 2019; 90: 20-9.
8. Turgut N, Varol SaraÇoglu G, Kat S, et al. An epidemiologic investigation of amyotrophic lateral sclerosis in Thrace, Turkey, 2006-2010. Amyotroph Lateral Scler Frontotemporal Degener 2019; 20: 100-6.
9. Uysal H, Taghiyeva P, Türkay M, Köse F, Aktekin M. Amyotrophic lateral sclerosis in Antalya, Turkey. A prospective study, 2016-2018 [published online ahead of print, 2020. Amyotroph Lateral Scler Frontotemporal Degener 2020; 1-7.
10. Brylev L, Ataulina A, Fominykh V, et al. The epidemiology of amyotrophic lateral sclerosis in Moscow (Russia). Amyotroph Lateral Scler Frontotemporal Degener 2020; 21: 410-5.
11. Argyriou AA, Polychronopoulos P, Papapetropoulos S, et al. Clinical and epidemiological features of motor neuron disease in south-western Greece. Acta Neurol Scand 2005; 111: 108-13.
12. Li TM, Alberman E, Swash M. Comparison of sporadic and familial disease amongst 580 cases of motor neuron disease. J Neurol Neurosurg Psychiatry 1988; 51: 778-84.
13. Camu W, Khoris J, Moulard B, et al. Genetics of familial ALS and consequences for diagnosis. French ALS Research Group. J Neurol Sci 1999; 165 Suppl 1: 21-6.
14. Chiò A, Logroscino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology 2013; 41: 118-30.
15. Longinetti E, Wallin AR, Samuelson K, et al. The Swedish motor neuron disease quality registry. Amyotroph Lateral Scler Frontotemporal Degener 2018; 19: 528-37.
16. Leighton DJ, Newton J, Stephenson LJ, et al. Changing epidemiology of motor neurone diseases in Scotland. J Neurol 2019; 266: 817-25.
17. Aktekin MR, Uysal H. Epidemiology of Amyotrophic Lateral Sclerosis. Turk J Neurol 2020; 26: 187-96
18. Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. Brain 1995; 118: 707-19.
19. Piemonte and Valle d'Aosta Register for Amyotrophic Lateral Sclerosis (PARALS). Incidence of ALS in Italy: evidence for a uniform frequency in Western countries. Neurology 2001; 56: 239-44.
20. Li TM, Alberman E, Swash M. Clinical features and associations of 560 cases of motor neuron disease. J Neurol Neurosurg Psychiatry 1990; 53: 1043-5.
21. Beghi E, Millul A, Micheli A, Vitelli E, Logroscino G; SLALOM Group. Incidence of ALS in Lombardy, Italy. Neurology 2007; 68: 141-5.
22. Ragonese P, Cellura E, Aridon P, et al. Incidence of amyotrophic lateral sclerosis in Sicily: A population based study. Amyotroph Lateral Scler 2012; 13: 284-7.
23. .Chen L, Zhang B, Chen R, et al. Natural history and clinical features of sporadic amyotrophic lateral sclerosis in China. J Neurol Neurosurg Psychiatry 2015; 86: 1075-81.
24. Jun KY, Park J, Oh KW, et al. Epidemiology of ALS in Korea using nationwide big data. J Neurol Neurosurg Psychiatry 2019; 90: 395-403.
25. Lee CT, Chiu YW, Wang KC, et al. Riluzole and prognostic factors in amyotrophic lateral sclerosis long-term and short-term survival: a population-based study of 1149 cases in Taiwan. J Epidemiol 2013; 23: 35-40.
26. Dorst J, Chen L, Rosenbohm A, et al. Prognostic factors in ALS: a comparison between Germany and China. J Neurol 2019; 266: 1516-25.

27. Kacem I, Sghaier I, Bougatef S, et al. Epidemiological and clinical features of amyotrophic lateral sclerosis in a Tunisian cohort. Amyotroph Lateral Scler Frontotemporal Degener 2020; 21: 131-9.

28. Marin B, Logroscino G, Boumediene F, et al. Clinical and demographic factors and outcome of amyotrophic lateral sclerosis in relation to population ancestral origin. Eur J Epidemiol 2016; 31: 229-45.

29. Louwerse ES, Visser CE, Bossuyt PM, Weverling GJ. Amyotrophic lateral sclerosis: mortality risk during the course of the disease and prognostic factors. The Netherlands ALS Consortium. J Neurol Sci 1997; 152 Suppl 1:10-7.

30. Chiò A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. Amyotroph Lateral Scler 2009; 10: 310-23.

31. Stevic Z, Kostic-Dedic S, Peric S, et al. Prognostic factors and survival of ALS patients from Belgrade, Serbia. Amyotroph Lateral Scler Frontotemporal Degener 2016; 17: 508-14.

32. Corcia P, Pradat PF, Salachas F, et al. Causes of death in a post-mortem series of ALS patients. Amyotroph Lateral Scler 2008; 9: 59-62.

Original Article

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Extraspinal incidental findings and reporting rates at lumbar spine magnetic resonance imaging: more than a spinal examination?

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ABSTRACT

Aim: To reveal the prevalence characteristics of extraspinal findings incidentally detected in lumbar spinal MRI examinations, determine their rate of reporting status, and analyze the findings in terms of clinical significance and patient benefit to help prevent possible medicolegal and ethical problems.

Material and Method: A total of 2,912 lumbar MRI examinations were retrospectively reviewed. The extraspinal findings were identified and analyzed according to their clinical significance. MRI examination reports were analyzed and whether extraspinal findings were included in these reports was determined.

Results: The study included a total of 2,912 patients, of whom 41% (n=1,195) were male and 59% (n=1,717) were female. The mean age of all patients was 48.25±15.92 (8-90) years. The mean age of men was 47.31±16.96 (9-90) and that of women was 48.91±15.12 (8-90) years. Extraspinal findings were present in 29% (n=844) of the patients and absent in 71% (n=2,068). The number of extraspinal findings 1 for 25.10% (n=731) of the patients, 2 in 3.61% (n=105), 3 in 0.24% (n=7), and 4 in 0.03% (n=1), with the total number being determined as 966.

Conclusion: Lumbar MRI images should be more carefully examined during the reporting stage and clinical evaluation in order to prevent possible morbidity-mortality situations by making accurate and early referrals in patient management and to avoid ethical-judicial problems that physicians may face due to the inability to recognize existing pathologies that may be outside the targeted area.

Keywords: Lumbar, magnetic resonance imaging, extraspinal, spinal

INTRODUCTION

Low back pain is one of the common complaints in society, and although the incidence of chronic low back pain has been reported as 23%, it is estimated that the probability of experiencing low back pain during a lifetime reaches 84% (1). Low back pain is mostly caused by the musculoskeletal system (2). Lumbar magnetic resonance imaging (MRI) is a frequently preferred imaging method in patients presenting with this complaint since it allows for the high spatial resolution and does not contain radiation (3). The use of computed tomography and MRI as diagnostic methods in patients with low back pain is becoming increasingly common (4).

Incidental findings (IFs) refer to findings that are unexpectedly detected during a radiological examination undertaken for an unrelated complaint in asymptomatic patients. In recent years, digital and technical developments in the evaluation of radiological examinations have led to a significant increase in the frequency of IFs (5).

A restricted field of view (FOV) is used in lumbar spinal MRI, and diagnostic images include especially spinal and paraspinal areas (6). A narrow FOV facilitates the focus of the attention of the radiologist reporting the images and the clinician requesting the examination on the spine, which is considered to be the primary source

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of pathology, and largely excludes abdominopelvic structures. However, FOV, which is used in lumbar MRI protocols in many radiology departments, can also display other elements, primarily those of the urogenital system, as well as abdominal main vascular structures, lymphatic system elements, and partially the peritoneal organs. Therefore, it is crucial to include extraspinal abdominopelvic pathologies observed in diagnostic images in radiology reports for both radiologists and other clinicians to prevent medicolegal problems.

This study aimed to reveal the prevalence characteristics of extraspinal IFs detected in lumbar spinal MRI examinations, to determine the reporting rates, and to analyze the findings in terms of clinical significance and patient benefit. Thus, the focus was to prevent possible medicolegal and ethical problems by increasing the awareness of both radiologists and clinicians that request an MRI examination concerning extraspinal IFs.

MATERIAL AND METHOD

After obtaining the approval of the Hitit University, Clinical Researchs Ethics Committe (Date: 26.08.2020, Decision No: 2020.07.03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was performed by retrospectively evaluating the MRI images and reports of lumbar spinal MRI examinations of patients that presented to the outpatient clinic with the complaint of low back pain and were followed up and treated with a diagnosis of discopathy and/or spinal pathologies. Lumbar MRI images were re-examined using the hospital Picture Archiving Communication System (PACS) by a radiologist with 12 years of experience in musculoskeletal system examinations, who was blinded to the previous radiology reports of the patients. Spinal findings were not noted in the re-evaluation, and extraspinal findings were recorded in axial and sagittal images. Simultaneously, the MRI examination reports were examined using the hospital automation system by another blinded physician independently from the radiologist that performed the re-examination, and the presence and variety of extraspinal findings were noted. For the study, a total of 3,135 lumbar MRIs were initially examined over the PACS system, but 223 were excluded from the study due to repeated scans or previous diagnoses related to the extraspinal findings included in FOV in the MRI examinations. For the remaining 2912 patients, demographic characteristics, namely patient age and gender were recorded. The detected extraspinal findings were categorized in terms of clinical significance according to the Modified Computed Tomography Colonography Reporting and Data System (C-RADS), which was previously used in studies investigating IFs (7). According to this classification, anatomical variations were included in the C-RADS E1 category, findings that were clinically insignificant or did not require an additional examination for diagnosis in C-RADS E2, those that could not be fully characterized and required a further examination to demonstrate their clinical significance in C-RADS E3, and other findings of clinical significance requiring specialist field consultation and additional radiological or pathological examinations in C-RADS E4. Then, the re-examination records and the first MRI reports obtained from the hospital automation system were compared in terms of the rate of IF reporting.

MRI Technique

MRI examinations were performed using a 1.5-T MRI device (General Electric, GE Medical System, Milwaukee, WI, USA) with a 32-channel spinal coil. Our routine lumbar spinal MR protocol includes sagittal T1-weighted; repetition time (TR)/echo time (TE), 496/9,8 ms; matrix, 288x256; FOV,34 cm; echo train length (ETL), 3, sagittal T2-weighted; TR/TE, 2500/110 ms; matrix, 288x256; FOV 32 cm; ETL, 23, and axial T2-weighted; TR/TE 3138/102 ms; matrix, 256x224; FOV, 24 cm; ETL, 23) sequences. The axial section images were taken between the L1 and S1 vertebrae. In all sequences, the slice thickness was 3 mm, the inter-slice gap was 1mm, and the number of excitations was 4. A presaturation band was only applied to the sagittal series. Some examples of extraspinal findings are presented in **Figure 1,2,3** and **4**.

Statistical Analysis

The statistical analysis of the data collected in our study was performed with SPSS (version 22, SPSS Inc., Chicago, IL, USA). The descriptive statistics of continuous variables obtained by measurements were reported using mean±standard deviation (min-max) values. Categorical variables were presented as numbers (n) and percentages (%).

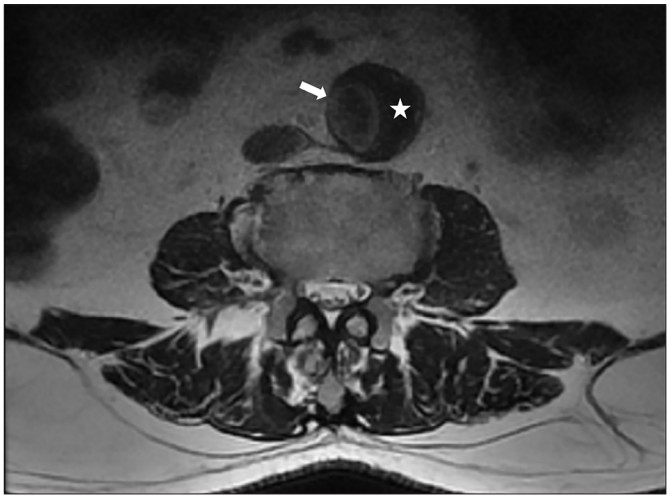

Figure 1. Abdominal aortic aneurysm (arrow) and mural thrombus (star) narrowing the lumen of the aorta in a crescent fashion in T2-weighted axial images in lumbar spinal MRI examination.

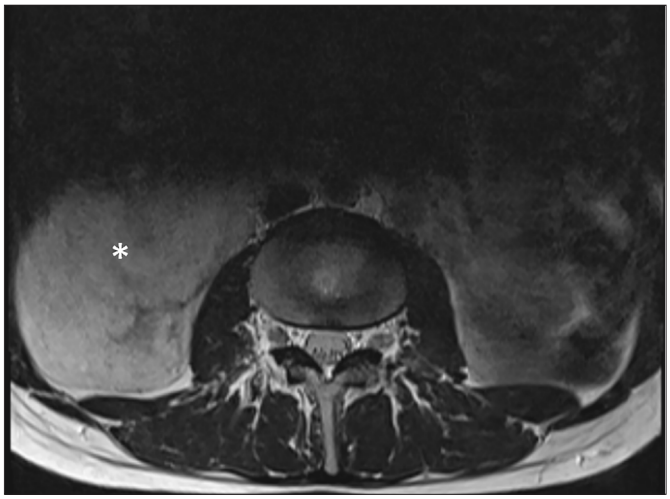

Figure 2. Hyperintense mass appearance of a giant angiomyolipoma in the right kidney (asterisk) in T2-weighted axial images in lumbar spinal MRI examination.

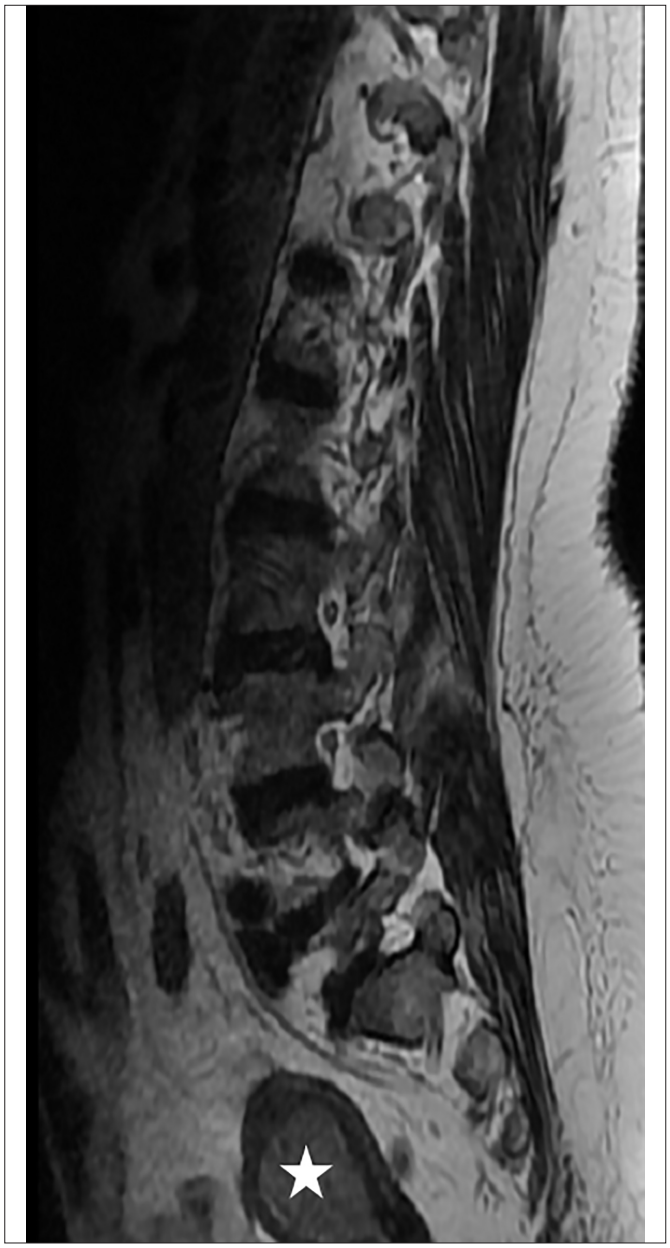

Figure 3. Postmenopausal endometrial hyperplasia (star) in the T2-weighted sagittal image.

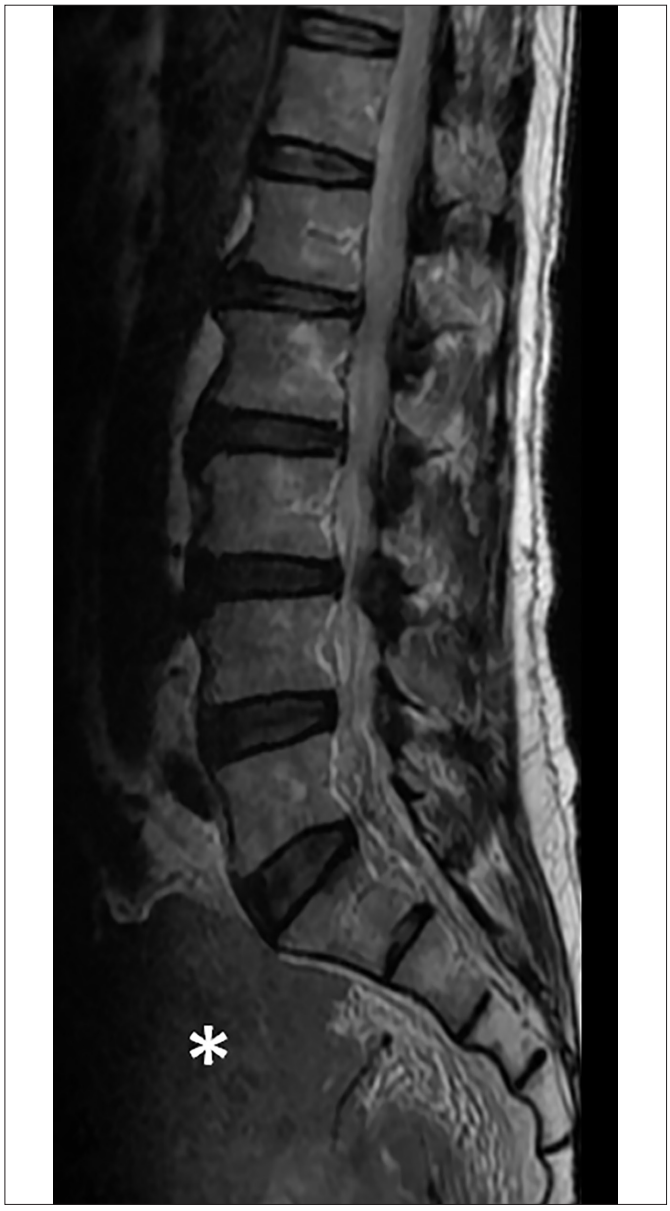

Figure 4. Pelvic mass (asterisk) in the T2-weighted image.

RESULTS

The study included a total of 2,912 patients, of whom 41% (n=1,195) were male and 59% (n=1,717) were female. The mean age of all patients was 48.25±15.92 (8-90) years. The mean age of men was 47.31±16.96 (9-90) years and that women was 48.91±15.12 (8-90) years. Extraspinal IFs were present in 29% (n=844) of the patients and absent in 71% (n=2,068). The number of extraspinal IFs was 1 for 25.10% (n=731) of the patients, 2 for 3.61% (n=105), 3 for 0.24% (n=7), and 4 for 0.03% (n=1). The total number of extraspinal IFs was 966. **Table 1** presents the frequency and percentages of extraspinal IFs categorized according to C-RADS in the study cohort and show their distribution by gender. The frequency and rates of the C-RADS categories among the patients in the study cohort and among those with extraspinal IFs are given in **Table 2**, and the rates of extraspinal IFs included in radiology reports are given in **Table 3** according to their C-RADS categories.

Table 1. Frequency and percentages of extraspinal IFs categorized according to C-RADS in the study cohort and show their distribution by gender

Category	Finding	Number (n)	Rate (%)	Male (n)	Female (n)
C-RADS E1	Variational findings	234	24.23	73	161
C-RADS E2	Unilateral renal atrophy	30	3.11	12	18
	Unilateral solitary kidney	12	1,24	5	7
	Renal stone	6	0.62	4	2
	Polycystic kidney disease	9	0.93	4	5
	Unilateral renal cyst	186	19.26	112	74
	Bilateral renal cyst	39	4,04	25	14
	Single uterine myoma	88	9.11	0	88
	Multiple uterine myomas	9	0.92	0	9
	Ovarian cyst	84	8.70	2	82
	Cavitary intrauterine device	46	4.76	0	46
	Migrating intrauterine device	2	0.21	0	2
	Benign prostate hyperplasia	36	3.73	21	15
	Nabothian cyst	45	4.66	0	45
	Submucosal myoma	1	0.10	0	1
	Transplanted kidney	1	0.10	1	0
	Gallbladder stone	3	0.31	0	3
	Uterine cervical myoma	2	0.21	2	0
Total		599	62.01	188	411
C-RADS E3	Paraaortic lymph node[a]	7	0.72	1	6
	Bilateral renal atrophy	3	0.31	1	2
	Hydroureteronephroses	30	3.10	15	15
	Liver lesion[b]	5	0.52	1	4
	Common bile duct dilatation[c]	6	0.62	1	5
	Subendometrial cyst	2	0.21	0	2
	Pelvic free fluid	2	0.21	0	2
	Bladder globus	1	0.10	0	1
	Ectatic abdominal aorta[d]	5	0.52	4	1
Total		61	6.31	23	38
C-RADS E4	Aortic aneurism[e]	5	0.52	5	0
	Paraaortic lymphadenomegaly[f]	32	3.31	14	18
	Renal mass	4	0.41	3	1
	Surrenal mass	9	0.93	1	8
	Pelvic mass	8	0.83	2	6
	Ovarian postmenopausal cystic lesion	6	0.62	0	6
	Postmenopausal endometrial hyperplasia	5	0.52	0	5
	Bladder wall thickening	2	0.21	2	0
	Postoperative recurrent lymphadenomegaly	1	0.10	0	1
Total		72	7.45	27	45
Total		**966**	**100.00**	**311**	**655**

[a]: Lymph node smaller than 10 mm in diameter, [b]: Hypertense liver lesion on T2-weighted images, [c]: Common bile duct diameter greater than 6 mm, [d]: Abdominal aorta diameter between 26 mm-30 mm, [e]: Abdominal aorta diameter greater than 30 mm, [f]: Lymph node larger than 10 mm in diameter

Table 2. The frequency and rates of the C-RADS categories among the patients in the study cohort and among those with extraspinal IFs

C-RADS category	Number of Patients	Age Mean ±SD (min-max)	Ratio in the whole sample (%)	Ratio among the patients with extraspinal IFs (%)	Ratio among the extraspinal IFs (%)
CRADS-E1	221	46.03±14.66 (19-82)	7.5	24.9	24,23
CRADS-E2	540	54.61±15.20 (15-90)	18.3	60.9	62,01
CRADS-E3	55	55.63±16.15 (18-82)	1.9	6.2	6,31
CRADS-E4	71	56.84±15.94 (19-88)	2.4	8	7,45

SD: Standard deviation, IF: incidental finding

Table 3. Rates of extraspinal IFs included in radiology reports

Category	Reporting status	Number	Percentage
C-RADS E1	Unreported	189	80.8
	Reported	45	19.2
	Total	234	100.0
C-RADS E2	Unreported	340	56.8
	Reported	259	43.2
	Total	599	100.0
C-RADS E3	Unreported	33	54.1
	Reported	28	45.9
	Total	61	100.0
C-RADS E4	Unreported	46	63.9
	Reported	26	36.1
	Total	72	100.0

DISCUSSION

IFs in imaging are mostly asymptomatic abnormalities that differ from expected pathologies and are typically found detected radiological examinations (2, 8). Advances in the radiological image processing technology and digital evaluation have increased the frequency and variety of IFs detected by different radiological modalities (9). This situation would also naturally increase the rate of variational or pathological findings, which are not related to the system examined to be included in radiology reports. Such findings present various practical and ethical problems related to the clinical management of patients for each branch. In medical practice today, many clinical disciplines are divided into specific sub-disciplines; therefore, the field of interest of the physician in clinical practice is narrowing. However, the need for a multidisciplinary approach for many diseases, the limited contribution of some symptoms to differential diagnosis, and the complex symptom characteristics of many disease groups can complicate the diagnosis process. In addition, it is known that radiological methods, which are among the most important diagnostic tools in clinical practice, are frequently requested to visualize a specific organ or system, and it remains controversial how much the clinician should be involved in the diagnosis of other pathologies that are not related to their patients' symptoms or within their range of expertise. For radiologists, the necessity to report pathological findings observed in the field of imaging, even if such examination is not basically within the expected radiological results, constitutes an ethical issue, as well as having a forensic aspect.

Lumbar spinal MRI is the most commonly used diagnostic radiological method in patients with low back pain in the presence of radiculopathy, discopathy or physical examination findings indicating degenerative spine diseases. Many extraspinal pathologies can be detected in the lumbar MRI images of patients. These extraspinal IFs can sometimes be more important than spinal pathologies, resulting in changes in the clinical management of the patient such as recurrence of renal cell carcinoma (10,11). This situation having legal implications for both the clinician requesting the examination and the radiologist.

In the current study, extraspinal IFs were found in 29% (n=844) of the patients. This rate was reported as 19.8% in a study that examined the lumbar MRI images of 1,278 patients in terms of extraspinal IFs, but the authors stated that the rate they detected was lower than the literature since they did not record small benign findings (5). In a similar study including 3,000 patients, the rate of extraspinal IFs was reported as 68.7% (12). In contrast, a study analyzing the frequency and clinical significance of abdominopelvic extraspinal IFs in lumbar MRIs recorded this rate to be 33.2% and suggested that it was consistent with the literature. The authors also noted that the 68.7% rate that had been reported by the previous study was significantly higher compared to other studies (6). The extraspinal IFs found in our study was in agreement with the literature, except for these two studies.

The extraspinal IFs detected in our study were categorized according to the C-RADS system based on their clinical significance. Extraspinal IFs in the C-RADS E1 category were detected in 7.5% of the patients included in the study. Among all extraspinal IFs, the rate of C-RADS E1 findings was 24.23%. Lesions in this category were evaluated as normal variants, and their reporting rate was 19.2%. Although normal variant findings are evaluated in a subcategory in terms of clinical significance, care should be taken considering the possibility of medical problems that may occur or surgical procedures that may be required later.

We found 599 C-RADS E2 category findings in 540 of the patients included in the study, and therefore this category constituted the largest group among all extraspinal IFs (62.01%). C-RADS E2 findings constituted 18.3% of all patients included in the study and 60.9% of those with extraspinal IFs, which is similar to the literature (13). Although the E2 group findings in the C-RADS system are categorized as clinically insignificant since they do not require an additional examination for diagnosis, it may be necessary to inform the patient about some of these findings and provide guidance in terms of treatment options. For example, when gallbladder stone disease is detected in lumbar MRI, although it has a high diagnostic accuracy rate, the patient should be made aware that he/she may require gastroenterological surgery in future. For this reason, it is of great importance to identify C-RADS E2 category findings and share them with the patient. In our study, the rate of inclusion of these findings in lumbar MRI reports was found to be 43.2%. This shows that more than half of these findings were not reported, and we consider that this ratio should be increased.

C-RADS E3 category findings occur due to possible benign causes, and additional investigations are required to fully reveal their etiology and adequately characterize them. In our study, 61 (6.31%) E3 category findings were detected constituting 6.31% of all extraspinal IFs. In a previous study, 25.9% of all extraspinal IFs were reported to be in the E3 category (14). However, C-RADS is not a special classification system for MRI examinations; it categorizes IFs detected in various procedures such as diagnostic radiology and diagnostic endoscopy based on basic principles followed by researchers in similar studies. Therefore, we consider that these proportional differences may be due to the inclusion of some findings in different groups according to the researchers' evaluation. In our study, the reporting rate of C-RADS E3 findings was found to be 45.9%. However, it should be kept in mind that radiological findings with a high probability of developing secondary to benign causes, including hydroureteronephrosis and common bile duct dilatation may be related to malignancies, and their etiology should be revealed. For this reason, we considered the reporting rate of the E3 category findings to be insufficient, and we strongly emphasize the need to include them in MRI reports.

In studies conducted with similar patient groups, lesions in the C-RADS E4 group were detected at an average rate of around 5% among all extraspinal IFs (12,13). In our study, this rate was 7.45%, and the patients with E4 group extraspinal IFs constituted 2.4% (n=71) of all patients included in the study. E4 group extraspinal IFs mostly require malignancy exclusion. In addition, diagnosis and treatment processes should be initiated before the development of complications that may result in mortality, such as an abdominal aortic aneurysm. In this process, clinician-radiologist cooperation is extremely important for the management of patients with E4 extraspinal IFs which we detected at a considerable rate of 7.45%. The reporting rate of E4 group findings in MRI reports was 36.1%, and it was determined that this category was reported less frequently compared to the E2 and E3 groups. It is clear that lesions in this group are of critical importance with early diagnosis and treatment steps, and thus clinicians should be more careful in terms of possible E4 group findings that are not included in the MRI report.

In a patient presenting with low back pain, the clinician should also evaluate non-spinal causes and cooperate with the radiologist. With a systematic approach, the radiologist should carefully evaluate the spinal area, then the extraspinal area, and report all findings that are considered to be significant or insignificant. Although the inclusion of extraspinal IFs in the MRI report does not constitute a legal problem, it may lead to additional stress for the patient. However, it can also help reveal life-threatening situations that can reduce patient morbidity and mortality, as well as preventing other legal problems.

The single-center and retrospective nature of the study can be considered as negative aspects, but the results are important in revealing the necessity of a systematic evaluation of spinal and non-spinal structures in lumbar MRI images. We consider that multi-center prospective studies can better identify the prevalence and severity of this situation.

CONCLUSION

Lumbar MRI images should be more carefully examined during the reporting stage and clinical evaluation in order to prevent possible morbidity-mortality situations by making accurate and early referrals in patient management and to avoid ethical-judicial problems that physicians may face due to the inability to recognize existing pathologies outside the targeted area.

ETHICAL DECLARATIONS

Ethics Committee Approval: Hitit University, Clinical Researchs Ethics Committe (Date: 26.08.2020, Decision No: 2020.07.03).

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. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. The lancet 2012; 379: 482-91.
2. Ibrahim H, Elsadawy MEI. Incidental findings in lumbar spine MRI: their prevalence and potential impact on patient management. Egyptian J Radiol Nuclear Med 2019; 50: 1-5.
3. Roudsari B, Jarvik JG. Lumbar spine MRI for low back pain: indications and yield. AJR Am J Roentgenol 2010; 195: 550-9.
4. Weiner DK, Kim Y-S, Bonino P, Wang T. Low back pain in older adults: are we utilizing healthcare resources wisely? Pain Med 2006; 7: 143-50.
5. Tuncel SA, Çaglı B, Tekataş A, Kırıcı MY, Ünlü E, Gençhellaç H. Extraspinal incidental findings on routine MRI of lumbar spine: prevalence and reporting rates in 1278 patients. Korean J Radiol 2015; 16: 866.

6. Maxwell A, Keating D, Nickerson J. Incidental abdominopelvic findings on expanded field-of-view lumbar spinal MRI: frequency, clinical importance, and concordance in interpretation by neuroimaging and body imaging radiologists. Clin Radiol 2015; 70: 161-7.
7. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: a consensus proposal. Radiology 2005; 236: 3-9.
8. Sobhan M, Samiee M, Asgari Y, Ahmadi M. Incidental findings of the lumbar spine at MRI in patients diagnosed with discopathy. Int J Med Imaging 2016; 4: 44.
9. Wagner SC, Morrison WB, Carrino JA, Schweitzer ME, Nothnagel H. Picture archiving and communication system: effect on reporting of incidental findings. Radiology 2002; 225: 500-5.
10. Dilli A, Ayaz UY, Turanlı S, et al. Incidental extraspinal findings on magnetic resonance imaging of intervertebral discs. Arch Med Sci 2014; 10: 757.
11. Park H-J, Jeon Y-H, Rho M-H, et al. Incidental findings of the lumbar spine at MRI during herniated intervertebral disk disease evaluation. AJR Am J Roentgenol 2011; 196: 1151-5.
12. Quattrocchi CC, Giona A, Di Martino AC, et al. Extra-spinal incidental findings at lumbar spine MRI in the general population: a large cohort study. Insights Imaging 2013; 4: 301-8.
13. Semaan HB, Bieszczad JE, Obri T, et al. Incidental Extraspinal Findings at Lumbar Spine Magnetic Resonance Imaging. Spine 2015; 40: 1436-43.
14. Lee SY, Landis MS, Ross IG, Goela A, Leung AE. Extraspinal findings at lumbar spine CT examinations: prevalence and clinical importance. Radiology 2012; 263: 502-9.

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The association between urine pH and abnormal glucose tolerance in adults

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ABSTRACT

Aim: Urine Ph (U-pH) is a clinical indicator of acid excretion in the urine and acid load in the diet. The association between low U-pH and net acid secretion with obesity, metabolic syndrome, diabetes, chronic kidney disease, and uric acid nephrolithiasis was showed. The aim of this study is to evaluate the U-pH in patients with different glucose tolerance statuses.

Material and Method: This study was designed as single-center, retrospective, and cross-sectional. A total of 1666 subjects (male/female: 531/1135) were divided into three groups according to their oral glucose tolerance test (OGTT) results: group 1=normal glucose tolerance (NGT), group 2=prediabetes, group 3=T2DM. Then subjects were divided into five groups according to their OGTT results: group 1=NGT, group 2=impaired fasting glucose (IFG), group 3=isolated impaired glucose tolerance (IGT), group 4=both IFG and IGT, and group 5=T2DM. Additionally, patients were divided into three groups according to their glycated hemoglobin (HbA1c) results: group 1=NGT, group 2=prediabetes, and group 3=T2DM. U-pH values and other outcomes were compared between groups.

Results: Age, male gender, hemoglobin, creatinine, triglycerides, and OGTT groups showed significant association with low U-pH through univariate logistic regression analyses. In model 1 (with OGTT 3 groups), it was found that creatinine (OR: 3.471; 95% CI: 1.377-8.749; p=0.008) and triglycerides (OR: 1.001; 95% CI: 1-1.003; p=0.013) were positively associated with low U-pH. Patients with T2DM (OR:1.437; 95% CI: 1.015-2.035; p=0.041) had higher risk for low U-pH compared to patients with NGT. In Model 2 (with OGTT 5 groups), creatinine (OR:3.423; 95% CI: 1.354-8.654; p=0.009) and triglycerides (OR:1.001; 95% CI: 1-1.003; p=0.014) were identified as independent predictive factors associated with low U-pH. Patients with IFG+IGT (OR:1.522; 95% CI: 1.083-2.138; p=0.015) and T2DM (OR:1.447; 95% CI: 1.022-2.049; p=0.037) had higher risk for low U-pH compared to patients with NGT.

Conclusion: In this study, the frequency of diabetes was found to be increased in patients with low U-pH. More detailed clinical studies are needed to evaluate whether different glucose tolerance statuses such as NGT, IFG, IGT, and T2DM are associated with U-pH.

Keywords: Urine pH, glucose, prediabetes, diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a frequent chronic disease and has reached an epidemic proportion worldwide. Diabetes, which is expected to reach 4.4% in 2030, its prevalence continues to increase, and the total number of patients with diabetes mellitus will reach 366 million by 2030 (1). Diabetes is often associated with protein and fat metabolic disorders, and electrolyte and acid-base imbalance. The frequency of eye, heart or renal vascular disease in diabetic patients is higher than in healthy subjects (2,3). Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are the two main components of prediabetes. Prediabetes is a transition process from normal glucose tolerance (NGT) to diabetes, which represents a state that often progresses to overt diabetes within a few years, and may be associated with an increased risk of micro and macrovascular complications (4,5). IFG is defined as the 0-hour plasma glucose level in the oral glucose tolerance test (OGTT) from 100 mg/dL to 125 mg/dL. IGT is a condition defined as 2.hour plasma glucose level ranging from 140 mg/dL to 199 mg/dL in OGTT (6). The level of glycated hemoglobin (HbA1C) ranging from 5.7% to 6.4% is another prediabetic condition, ≥6.5 diabetes ≤5.7 is considered as normal glucose homeostasis (7).

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In the human body, acidic substances consisting of intracellular metabolic events and dietary nutritional sources are excreted through the lungs and kidneys. Volatile acids are excreted from the lungs via the respiratory tract as such CO_2 (15000 meq per day), while nonvolatile acids are excreted from the kidneys in the urine (1meq/kg/day per day) (8). Urine Ph is a clinical indicator of acid excretion in the urine and acid load in the diet. Also, several studies revealed the association between low urine Ph (U-pH) and net acid secretion with obesity, metabolic syndrome, T2DM, obesity, insulin resistance, chronic kidney disease, and uric acid nephrolithiasis (9–13). The role of acid-base imbalance in patients with diabetes is mediated by insulin resistance (14,15). Previous studies reported the association between diet acid load with metabolic syndrome, hypertension, and T2DM (16–19). In a study with a large number of patients, it was shown that the risk of developing diabetes in male patients with U-pH≤ 5 over a 5-year period significantly increased compared to those with U-pH≥5 (20). However, in Turkish patients, no study has previously been published that has investigated the relationship between U-pH, which is a useful marker for acid load, and OGTT findings.

We planned to examine U-pH values in participants with different glucose tolerance statuses to evaluate whether OGTT findings such as NGT, IFG, IGT, and T2DM are associated with U-pH.

MATERIAL AND METHOD

The study was carried out with the permission of Akdeniz University Faculty of Medicine Clinical Researchs Ethics Committee (Date: 08.07.2020, Decision No: 490). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

This study was designed as single-center, retrospective, and cross-sectional. The study consisted of outpatients who presented to Akdeniz University Medical Faculty, Department of Internal Medicine outpatient clinic and were administered OGTT. Laboratory data were obtained from electronic patient files. The study included patients who were aged >40, had fasting blood glucose between 100-126 mg/dL, had a family history of diabetes mellitus, and symptoms of reactive hypoglycemia. Exclusion criteria for the study were lack of data for U-pH, patients using metformin and other oral antidiabetic agents due to insulin resistance, lack of data for serum creatinine, chronic liver disease, and chronic kidney disease at baseline. Furthermore, individuals who had gestational diabetes, acute or chronic inflammation, urinary infection, cardiovascular disease with corticosteroid treatment, malign disease, or other known chronic diseases were excluded from the study. After applying the inclusion and exclusion criteria, a total of 1666 subjects (male/female: 531/1135) who received between January 2015 and June 2020 were included in the study.

All individuals were divided into three groups according to the OGTT results, group 1=NGT, group 2=prediabetic, group 3=T2DM. Then, all individuals were divided into five groups based on the OGTT results, according to the World Health Organization diagnostic criteria for diabetes (6): group 1=NGT, group 2=IFG, group 3=IGT, group 4=both IFG and IGT, group 5=T2DM. Furthermore, individuals were divided into three groups based on the results of HbA1c: group 1=normal range (HbA1c <5.7%), group 2=prediabetic status (HbA1c: 5.7-6.4%), and group 3=T2DM (HbA1c ≥6.5%). Finally, participants were divided into three groups as normal, prediabetes, and T2DM by evaluating both OGTT and HbA1c results together.

The estimated glomerular filtration rate (eGFR) was calculated as follows based on CKD-EPI 2009 (Chronic Kidney Disease Epidemiologic Collaboration):eGFR=141 x min (Scr/k, 1) a x max (Scr/k, 1) -1,209 x0,993 Age x 1,018 [Women] x 1,159 [Black race]. -Scr=serum creatinine, k=0.7 for women and 0.9 for men, a=-0.329 for women and -0.411 for men. min=Scr/k minimum.

Statistics

Statistical analyzes were conducted by using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Normality assumptions were controlled by the Shapiro–Wilk test. Descriptive analyzes were presented using mean±SD, median (min-max) or n (%), where appropriate. Categorical data was analyzed using Pearson's chi-square. Kruskal Wallis test was used for comparison of nonparametric variables between groups and Bonferroni-Dunn test was used as a post hoc test for significant cases, while One-Way ANOVA with post hoc Tukey HSD test was used for parametric variables. Univariate and multivariate logistic regression analyzes were used to determine independent risk factors associated with low U-pH (pH=5.0). Odds ratio (OR) was reported with the corresponding 95% confidence intervals (95% CI). A p-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The mean age of the 1666 patients included in the study was 50.77±13.23 years, and 68.1% were women. When participants were divided into three groups according to their OGTT results as NGT, prediabetes, and T2DM; the mean age of the diabetic group and the percentage of male participants were higher than in the other

groups. Additionally, the creatinine, HbA1c, and 1st hour glucose values were higher in the diabetic group. eGFR was highest in the NGT group and lowest in the diabetic group (Table 1). The U-pH values of the diabetes and prediabetes groups were lower than those of the NGT group, while the percentage of patients with pH=5.0 was lower in the NGT group than in the other two groups. The CRP and triglyceride values of the prediabetes and diabetic groups were higher and the HDL values were lower (**Table 1**).

Relationship Between U-pH and OGTT

When the prediabetic group was divided into three groups, IGF, IGT, and IFG+IGT; while the eGFR values were highest in NGT group and lowest in the T2DM group (p<0.001). The percentage of male patients and serum creatinine in the IFG+IGT and diabetic group were higher than in the other groups (p<0.001). The HbA1c values of the IFG and IGT groups were similar. As the prevalence of diabetes increased, the glucose levels at the first hour also increased (p<0.001). The U-pH values of the IFG+IGT and T2DM groups were lower than those of the NGT group (p=0.007). The percentage of patients with pH 5.0 in the NGT group was lower than in the IFG+IGT and T2DM groups (p=0.026) (**Table 2**). Other biochemical parameters compared for the patients are shown in **Table 2**.

Relationship Between U-pH and HbA1c

The patients were divided into three groups according to their HbA1c values as <5.7 (n=531), 5.7-6.49 (n=1019), and ≥ 6.5 (n=116). There were no significant differences between the gender distributions (p=0.115) and the U-pH values (p=0.534) of the groups. It was observed that as the HbA1c level increased, the glucose levels in the first hour also increased (p<0.001). The hemoglobin (p=0.006) and eGFR (p<0.001) values of the group with HbA1c<5.7 were higher than the other two groups, and CRP (p<0.001), triglyceride (p=0.015), and uric acid (p=0.031) were lower. HDL was lower in the group with HbA1c≥6.5 (p=0.004) (**Table 3**).

Relationship Between U-pH and OGTT/HbA1c

The patients were divided into three groups according to their OGTT and HbA1c values such as NGT (n=240), prediabetes (n=1071), and T2DM (n=355). There was no significant difference between the groups in terms of albumin (p=0.206), and U-pH values (p=0.132). The hemoglobin value of the diabetic group was higher than that of the prediabetes group (p=0.017) and its creatinine was higher than that of the other two groups (p<0.001). It was observed that as the frequency of diabetes increased, the eGFR values decreased and the triglyceride values increased (p<0.001). The HDL of the diabetic group was lower than that of the NGT group (p=0.009) (**Table 4**).

Table 1. Comparison of patients' characteristics according to OGTT groups

Variables	Overall	NGT	Prediabetes	T2DM	p values
Number (%)	1666	532 (31.9)	826 (49.6)	308 (18.5)	-
Age (years)	50.77±13.23	45.72±14.34[a]	52.23±12.14[b]	55.57±11.16[c]	<0.001
Gender					
Male	531 (31.9)	149 (28)[a]	258 (31.2)[a]	124 (40.3)[b]	0.001
Female	1135 (68.1)	383 (72)	568 (68.8)	184 (59.7)	
Hemoglobin (g/L)	13.51±1.54	13.27±1.62[a]	13.55±1.45[b]	13.86±1.54[c]	<0.001
Creatinine (mg/dL)	0.75±0.16	0.72±0.15[a]	0.75±0.16[b]	0.78±0.16[c]	<0.001
eGFR (mL/min/1.73m²)	110.48 (65.9-188.76)	116.84 (70.72-162.11)[a]	109.03 (65.9-188.76)[b]	105.99 (67.51-144.95)[c]	<0.001
CRP (mg/dL)	0.27 (0-30.39)	0.18 (0-2.86)[a]	0.32 (0.01-30.39)[b]	0.35 (0.01-4.79)[b]	<0.001
Uric acid (mg/dL)	5.45±1.48	5.13±1.42	5.57±1.54	5.59±1.41	0.114
Triglycerides (mg/dL)	138 (30.62-1265.54)	124 (30.62-1020)[a]	141 (35-1265.54)[b]	150.68 (40-1201)[b]	<0.001
LDL (mg/dL)	134.9±37.23	132.82±38.59	135.55±36.54	136.46±36.86	0.430
HDL (mg/dL)	46.75 (18-109.7)	49.4 (23-109.7)[a]	46.05 (18-109.5)[b]	44.4 (21-90.2)[b]	0.001
Albumin (g/dL)	4.45 (2.9-5.65)	4.4 (3.64-5.18)	4.47 (2.9-5.65)	4.46 (3.78-5.14)	0.082
HbA1c (%)	5.9 (4-11.6)	5.7 (4-7)[a]	5.9 (4.2-7.1)[b]	6.2 (4.4-11.6)[c]	<0.001
<5.7	531 (31.9)	240 (45.1)[a]	253 (30.6)[b]	38 (12.3)[c]	<0.001
5.7-6.49	1019 (61.2)	285 (53.6)[a]	533 (64.5)[b]	201 (65.3)[b]	
≥6.5	116 (7)	7 (1.3)[a]	40 (4.8)[b]	69 (22.4)[c]	
1st hour glucose (mg/dL)	177.94±49	139.96 ±35.98[a]	188.42±37.19[b]	242.93±36.06[c]	<0.001
U-pH	5 (5-9)	5.5 (5-8.5)[a]	5 (5-8.5)[b]	5 (5-9)[b]	0.004
pH 5.0	864 (51.9)	247 (46.4)[a]	442 (53.5)[b]	175 (56.8)[b]	0.003
pH 5.5	237 (14.2)	82 (15.4)[a]	119 (14.4)[a]	36 (11.7)[a]	
pH 6.0	178 (10.7)	58 (10.9)[a]	90 (10.9)[a]	30 (9.7)[a]	
pH 6.5	178 (10.7)	62 (11.7)[a]	81 (9.8)[a]	35 (11.4)[a]	
pH ≥7	209 (12.5)	83 (15.6)[a]	94 (11.4)[a]	32 (10.4)[a]	

OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; T2DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c: glycated hemoglobin; U-pH, Urine pH
Data are presented as mean±SD, median (min-max), or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lower case letters in a row indicate statistically significant difference between groups.

Table 2. Comparison of patients' characteristics according to OGTT subgroups

Variables	NGT	Prediabetes IFG	Prediabetes IGT	Prediabetes IFG+IGT	T2DM	p values
Number (%)	532 (31.9)	371 (22.3)	148 (8.9)	307 (18.4)	308 (18.5)	-
Age (years)	45.72±14.34[a]	51.39±12.24[b]	51.14±13.06[b]	53.77±11.41[b,c]	55.57±11.16[c]	<0.001
Gender						
Male	149 (28)[a]	109 (29.4)[a]	35 (23.6)[a]	114 (37.1)[b]	124 (40.3)[b]	<0.001
Female	383 (72)	262 (70.6)	113 (76.4)	193 (62.9)	184 (59.7)	
Hemoglobin (g/L)	13.27±1.62[a]	13.52±1.45[a,b]	13.3±1.33[a,b]	13.7±1.48[b]	13.86±1.54[c]	<0.001
Creatinine (mg/dL)	0.72±0.15[a]	0.74±0.15[a]	0.74±0.17[a]	0.77±0.17[b]	0.78±0.16[b]	<0.001
eGFR (mL/min/1.73m²)	116.84 (70.72-162.11)[a]	109.49 (67.51-160.8)[b]	109.81 (72.66-154.67)[b]	107.9 (65.9-188.76)[b,c]	105.99 (67.51-144.95)[c]	<0.001
CRP (mg/dL)	0.18 (0-2.86)[a]	0.33 (0.01-30.39)[b]	0.35 (0.01-5.07)[b]	0.31 (0.01-6.39)[b]	0.35 (0.01-4.79)[b]	<0.001
Uric acid (mg/dL)	5.13±1.42	5.31±1.47	5.68±1.71	5.75±1.48	5.59±1.41	0.167
Triglycerides (mg/dL)	124 (30.62-1020)[a]	133 (35-1265.54)[a]	143.83 (47-1066)[b]	148.31 (38.94-743)[b]	150.68 (40-1201)[b]	<0.001
LDL (mg/dL)	132.82±38.59	135.4±37.41	138.28±36.24	134.4±35.63	136.46±36.86	0.654
HDL (mg/dL)	49.4 (23-109.7)[a]	48 (18-94.2)[a,b]	47.9 (21.9-102.3)[a,b]	44.1 (22-109.5)[b]	44.4 (21-90.2)[b]	0.002
Albumin (g/dL)	4.4 (3.64-5.18)	4.47 (3.37-5.65)	4.47 (3.79-5.17)	4.46 (2.9-5.16)	4.46 (3.78-5.14)	0.285
HbA1c (%)	5.7 (4-7)[a]	5.8 (4.2-7.1)[b]	5.86 (4.6-7.04)[b]	6 (4.7-6.88)[c]	6.2 (4.4-11.6)[d]	<0.001
<5.7	240 (45.1)[a]	128 (34.5)[b]	52 (35.1)[b]	73 (23.8)[c]	38 (12.3)[d]	<0.001
5.7-6.49	285 (53.6)[a]	226 (60.9)[a,b]	92 (62.2)[a,b]	215 (70)[b]	201 (65.3)[b]	
≥6.5	7 (1.3)[a]	17 (4.6)[b]	4 (2.7)[a,b]	19 (6.2)[b]	69 (22.4)[c]	
1st hour glucose (mg/dL)	139.96±35.98[a]	171.71±36.84[b]	184.57±28.99[c]	209.67±29.97[d]	242.93±36.06[e]	<0.001
U-pH	5.5 (5-8.5)[a]	5.5 (5-8.5)[a,b]	5 (5-8.5)[a,b]	5 (5-8)[b]	5 (5-9)[b]	0.007
pH 5.0	247 (46.4)[a]	183 (49.3)[a,b]	79 (53.4)[a,b]	180 (58.6)[b]	175 (56.8)[b]	0.026
pH 5.5	82 (15.4)[a]	67 (18.1)[a]	16 (10.8)[a]	36 (11.7)[a]	36 (11.7)[a]	
pH 6.0	58 (10.9)[a]	47 (12.7)[a]	17 (11.5)[a]	26 (8.5)[a]	30 (9.7)[a]	
pH 6.5	62 (11.7)[a]	32 (8.6)[a]	15 (10.1)[a]	34 (11.1)[a]	35 (11.4)[a]	
pH ≥7	83 (15.6)[a]	42 (11.3)[a]	21 (14.2)[a]	31 (10.1)[a]	32 (10.4)[a]	

OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; ; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c: glycated hemoglobin; U-pH, Urine pH
Data are presented as mean±SD, median (min-max), or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lowercase letters in a row indicate statistically significant difference between groups.

Table 3. Comparison of patients' characteristics according to HbA1c groups

Variables	<5.7	5.7-6.49	≥6.5	p values
Number (%)	531 (31.9)	1019 (61.2)	116 (7)	-
Age (years)	45.52±13.73[a]	53.12±12.45[b]	54.2±10.28[b]	<0.001
Gender				
Male	164 (30.9)	320 (31.4)	47 (40.5)	0.115
Female	367 (69.1)	699 (68.6)	69 (59.5)	
Hemoglobin (g/L)	13.7±1.51[a]	13.42±1.51[b]	13.41±1.79[b]	0.006
Creatinine (mg/dL)	0.74±0.15	0.75±0.17	0.77±0.16	0.084
eGFR (mL/min/1.73 m²)	116.39 (72.66-162.11)[a]	108.92 (65.9-188.76)[b]	106.94 (76.86-154.81)[b]	<0.001
CRP (mg/dL)	0.2 (0-30.39)[a]	0.32 (0-6.39)[b]	0.55 (0.08-2.13)[b]	<0.001
Uric acid (mg/dL)	5.12±1.55[a]	5.59±1.39[b]	5.93±1.65[b]	0.031
Triglycerides (mg/dL)	131.95 (30.62-1066)[a]	141.27 (35-1265.54)[b]	137 (40-442)[b]	0.015
LDL (mg/dL)	131.74±36.5	136.19±38.09	136.64±31.9	0.168
HDL (mg/dL)	47.48 (20.9-109.7)[a]	47.1 (18-109.5)[a]	41.2 (27-90.2)[b]	0.004
Albumin (g/dL)	4.42 (3.77-5.18)	4.45 (2.9-5.65)	4.51 (3.81-4.98)	0.863
HbA1c (%)	5.37 (4-5.69)[a]	6 (5.7-6.49)[b]	6.7 (6.5-11.6)[c]	<0.001
1st hour glucose (mg/dL)	159.25±45.65[a]	185.31±47.03[b]	217.79±50.16[c]	<0.001
U-pH	5 (5-9)	5 (5-8.5)	5 (5-8)	0.534
pH 5.0	270 (50.8)	533 (52.3)	61 (52.6)	0.735
pH 5.5	69 (13)	146 (14.3)	22 (19)	
pH 6.0	60 (11.3)	107 (10.5)	11 (9.5)	
pH 6.5	57 (10.7)	110 (10.8)	11 (9.5)	
pH ≥7	75 (14.1)	123 (12.1)	11 (9.5)	

eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c: glycated hemoglobin; U-pH, Urine pH
Data are presented as mean±SD, median (min-max), or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lowercase letters in a row indicate statistically significant difference between groups.

Table 4. Comparison of patients' characteristics according to OGTT-HbA1c combined groups

Variables	NGT	Prediabetes	T2DM	p values
Number (%)	240 (14.4)	1071 (64.3)	355 (21.3)	-
Age (years)	40.28±13.39[a]	51.61±12.66[b]	55.34±10.97[c]	<0.001
Gender				
Male	69 (28.7)[a]	323 (30.2)[a]	139 (39.2)[b]	0.004
Female	171 (71.3)	748 (69.8)	216 (60.8)	
Hemoglobin (g/L)	13.58±1.58[a,b]	13.43±1.49[a]	13.72±1.63[b]	0.017
Creatinine (mg/dL)	0.72±0.14[a]	0.74±0.16[a]	0.78±0.16[b]	<0.001
eGFR (mL/min/1.73 m²)	123.07 (84.54-162.11)[a]	110.2 (65.9-188.76)[b]	106.2 (67.51-154.81)[c]	<0.001
CRP (mg/dL)	0.16 (0-2.09)[a]	0.28 (0-30.39)[b]	0.36 (0.01-4.79)[b]	<0.001
Uric acid (mg/dL)	4.86±1.52[a]	5.55±1.43[b]	5.57±1.53[b]	0.035
Triglyserides (mg/dL)	115 (30.62-484.88)[a]	138.45 (35-1265.54)[b]	149.45 (40-1201)[c]	<0.001
LDL (mg/dL)	127.13±36.08[a]	136.04±37.85[b]	135.87±35.63[b]	0.027
HDL (mg/dL)	49.3 (26.1-109.7)[a]	47.1 (18-109.5)[a,b]	44.4 (21-90.2)[b]	0.009
Albumin (g/dL)	4.4 (3.77-5.18)	4.45 (2.9-5.65)	4.49 (3.78-5.14)	0.206
HbA1c (%)	5.3 (4-5.69)[a]	5.9 (4.2-6.49)[b]	6.3 (4.4-11.6)[c]	<0.001
1st hour glucose (mg/dL)	131.46±35.98[a]	176.68±40.59[b]	233.21±41.72[c]	<0.001
U-pH	5.5 (5-8.5)	5 (5-8.5)	5 (5-9)	0.132
pH 5.0	118 (49.2)	545 (50.9)	201 (56.6)	0.597
pH 5.5	36 (15)	157 (14.7)	44 (12.4)	
pH 6.0	24 (10)	120 (11.2)	34 (9.6)	
pH 6.5	26 (10.8)	113 (10.6)	39 (11)	
pH ≥7	36 (15)	136 (12.7)	37 (10.4)	

OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; T2DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c: glycated hemoglobin; U-pH, Urine pH
Data are presented as mean±SD, median (min-max), or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lowercase letters in a row indicate statistically significant difference between groups.

The patients were divided into five groups according to U-pH values of 5.0 (n=864), 5.5 (n=237), 6.0 (n=178), 6.5 (n=178) and ≥7 (n=209). There was no difference between the groups in terms of the combined group distribution of LDL-c, glucose in the first hour, HbA1c, and OGTT-HbA1c combined group distribution (**Table 5**). The mean age of the pH 5.5 group was lower than that of the pH 5.0 and 6.5 groups (p=0.007). In the pH 5.0 group, the percentage of male patients and normal OGTT was higher than in the pH≥7 group (p=0.032, p=0.026, respectively). Hemoglobin value was higher in the pH 5.5 group than the ≥7 group (p=0.042). Creatinine in the pH 5.0 group was higher (p<0.001). The lowest eGFR values were observed in the pH 5.0 and 6.5 groups (p=0.001). The uric acid value of the pH 5.5 group was higher than that of the pH 6.5 and grub ≥7 group (p=0.005). Triglyceride values were higher in the pH 5.0 and 6.5 group compared to the pH 6.0 and ≥7 group (p=0.003). HDL-c was lower in the pH 5.0 group than in the pH 6.0 and ≥7 group (p=0.004).

Logistic Regression Analysis

Age, male gender, hemoglobin, creatinine, triglycerides, and OGTT groups showed a significant association with low U-pH through univariate logistic regression analyzes. In model 1 (with OGTT 3 groups), it was found that creatinine (OR:3.471; 95% CI:1.377-8.749; p=0.008) and triglycerides (OR:1.001; 95% CI:1-1.003; p=0.013) were positively associated with low U-pH. Patients with T2DM (OR:1.437; 95% CI:1.015-2.035; p=0.041) had a higher risk of low U-pH compared to patients with NGT. In Model 2 (with OGTT 5 groups), creatinine (OR:3.423; 95% CI:1.354-8.654; p=0.009) and triglycerides (OR:1.001; 95% CI:1-1.003; p=0.014) were identified as independent predictive factors associated with low U-pH. Patients with IFG+IGT (OR:1.522; 95% CI:1.083-2.138; p=0.015) and T2DM (OR:1.447; 95% CI: 1.022-2.049; p=0.037) had a higher risk of low U-pH compared to patients with NGT (**Table 6**).

DISCUSSION

We present a study with a large number of subjects who had no chronic disease at baseline, its results showed that the level of U-pH was significantly associated with various glucose tolerance statuses.

Providing a fixed intracellular and extracellular pH level is essential for the body to perform its normal physiological function, and it is regulated by complex biological processes. Goel and Calvert have demonstrated that the systems that provide the balance of acid and base are made up of the intracellular and extracellular buffering systems, the respiratory system, and the urinary system (21). Additionally, all fats, carbohydrates, and proteins affect the pH of the body. As our body produces approximately 2-3 mEq/kg H^+ ions daily, changes in acid-base balance regulated by cellular metabolism are highly associated with diet components.

Table 5. Comparison of patients' characteristics according to U-pH groups

Variables	U-pH groups					p values
	pH 5.0	pH 5.5	pH 6.0	pH 6.5	pH ≥7.0	
Number (%)	864 (51.9)	237 (14.2)	178 (10.7)	178 (10.7)	209 (12.5)	
Age (years)	51.55±12.58[a]	48.35±14.72[b]	50.16±13.28[a,b]	52.03±13.04[a]	49.73±13.84[a,b]	0.007
Gender						
Male	296 (34.3)[a]	79 (33.3)[a,b]	53 (29.8)[a,b]	55 (30.9)[a,b]	48 (23)[b]	0.032
Female	568 (65.7)	158 (66.7)	125 (70.2)	123 (69.1)	161 (77)	
Hemoglobin (g/L)	13.55±1.51[a,b]	13.71±1.56[a]	13.39±1.53[a,b]	13.47±1.55[a,b]	13.26±1.57[b]	0.042
Creatinine (mg/dL)	0.76±0.16[a]	0.74±0.15[a,b]	0.74±0.16[a,b]	0.74±0.17[a,b]	0.7±0.15[b]	<0.001
eGFR (mL/min/1.73 m²)	109.49 (65.9-188.76)[a]	112.27 (71.56-162.11)[b]	112.39 (78.14-150.28)[b]	107.78 (70.81-157.68)[a]	113.34 (70.72-154.81)[b]	0.001
Uric acid (mg/dL)	5.49±1.56[a,b]	6.26±1.61[a]	5.62±1.38[a,b]	5.11±1.09[b]	4.9±1.21[b]	0.005
Triglycerides (mg/dL)	142.11 (33-1066)[a]	133.08 (35-743)[a,b]	131 (30.62-442)[b]	144.28 (31.08-1265.54)[a]	127 (35.78-1201)[b]	0.003
LDL (mg/dL)	133.77±37.3	136.18±40.05	133.47±36.07	138.21±36.48	136.49±35.47	0.699
HDL (mg/dL)	44.9 (18-109.7)[a]	45.9 (27-89.8)[a,b]	51 (20.9-109.5)[b]	47.75 (25.2-80)[a,b]	49.8 (21.9-102.1)[b]	0.004
HbA1c (%)	5.9 (4-11.2)	5.9 (4.2-10.6)	5.89 (4.4-11.6)	5.89 (4.3-7.71)	5.8 (4.2-7.75)	0.428
<5.7	270 (31.3)	69 (29.1)	60 (33.7)	57 (32)	75 (35.9)	0.735
5.7-6.5	533 (61.7)	146 (61.6)	107 (60.1)	110 (61.8)	123 (58.9)	
≥6.5	61 (7.1)	22 (9.3)	11 (6.2)	11 (6.2)	11 (5.3)	
1st hour glucose (mg/dL)	181.34±48.41	172.66±50.17	175.34±48.29	173.86±49.53	175.89±49.61	0.084
OGTT						
NGT	247 (28.6)[a]	82 (34.6)[a,b]	58 (32.6)[a,b]	62 (34.8)[a,b]	83 (39.7)[b]	0.026
IFG	183 (21.2)[a]	67 (28.3)[a]	47 (26.4)[a]	32 (18)[a]	42 (20.1)[a]	
IGT	79 (9.1)[a]	16 (6.8)[a]	17 (9.6)[a]	15 (8.4)[a]	21 (10)[a]	
IFG+IGT	180 (20.8)[a]	36 (15.2)[a]	26 (14.6)[a]	34 (19.1)[a]	31 (14.8)[a]	
T2DM	175 (20.3)[a]	36 (15.2)[a]	30 (16.9)[a]	35 (19.7)[a]	32 (15.3)[a]	
Combined groups						
NGT	118 (13.7)	36 (15.2)	24 (13.5)	26 (14.6)	36 (17.2)	0.597
Prediabetes	545 (63.1)	157 (66.2)	120 (67.4)	113 (63.5)	136 (65.1)	
T2DM	201 (23.3)	44 (18.6)	34 (19.1)	39 (21.9)	37 (17.7)	

OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; ; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c: glycated hemoglobin; U-pH, Urine pH
Data are presented as mean±SD, median (min-max), or n (%). ANOVA, Kruskal-Wallis test, Pearson chi-square test. Different lowercase letters in a row indicate statistically significant difference between groups.

Table 6. Univariate and multivariate logistic regression analysis for low U-pH (U-pH ≤5.0)

Variables	Univariate analysis		Model 1 with OGTT 3 groups		Model 2 with OGTT 5 groups	
	OR (95%CI)	P values	OR (95%CI)	p	OR (95%CI)	p values
Age (years)	1.009 (1.002-1.017)	0.012	1.002 (0.993-1.011)	0.644	1.002 (0.992-1.011)	0.724
Male Gender	1.257 (1.022-1.547)	0.030	0.959 (0.682-1.349)	0.811	0.954 (0.678-1.341)	0.785
Hemoglobin (g/L)	1.097 (1.021-1.178)	0.011	0.966 (0.88-1.059)	0.458	0.964 (0.879-1.058)	0.439
Creatinine (mg/dL)	3.27 (1.742-6.138)	<0.001	3.471 (1.377-8.749)	0.008	3.423 (1.354-8.654)	0.009
Triglycerides (mg/dL)	1.002 (1.001-1.003)	0.002	1.001 (1-1.003)	0.013	1.001 (1-1.003)	0.014
OGTT 3 groups						
NGT	Reference	-	Reference	-	-	-
Prediabetes	1.328 (1.067-1.652)	0.011	1.296 (0.994-1.689)	0.055	-	-
T2DM	1.518 (1.144-2.014)	0.004	1.437 (1.015-2.035)	0.041	-	-
OGTT 5 groups						
NGT	Reference	-	-	-	Reference	-
IFG	1.123 (0.861-1.465)	0.391	-	-	1.188 (0.866-1.632)	0.286
IGT	1.321 (0.917-1.903)	0.135	-	-	1.173 (0.763-1.804)	0.468
IFG+IGT	1.635 (1.231-2.172)	0.001	-	-	1.522 (1.083-2.138)	0.015
T2DM	1.518 (1.144-2.014)	0.004	-	-	1.447 (1.022-2.049)	0.037

OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; ; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, diabetes mellitus; OR, Odds ratio; CI,confidence intervals

The intracellular buffering system is managed by a system that uses proteins and organic phosphates for the regulation of acid-base balance. Intracellular buffering occurs by binding bicarbonate (HCO_3) and H+ ions and performing extracellular carbon dioxide (CO_2) and water (H_2O) secretion (22). Intracellular and extracellular buffering systems provide short-term solutions to alkalemia and acidemia. For this reason, there are supporting mechanisms such as the respiratory and urinary systems to regulate extracellular pH. When an increase in extracellular H^+ ions is felt, the respiratory system may accelerate respiration to remove CO_2, which is a weak acid, from the body. On the contrary, in the event of a decrease in the amount of H^+ ions, the brain chemosensors are stimulated to slow respiration and keep CO_2 in the body (23). The effect of the respiratory system is observed very quickly and it can change the pH level in hours or even minutes. The urinary system is much more complex and slow, and, for this reason, it takes hours and days for it to change H^+ ion levels during urination, excessive H^+ ions and ammonia are excreted into urine. The ammonia produced in renal tubular cells spreads in the intraluminal space and is bound to H^+ ions and provides excretion from the body in the acidosis period. Furthermore, potassium ions, calcium ions, and urinary phosphate are also excreted from the body by urine in the acute and chronic acidosis periods (8,24). As plasma bicarbonate has a buffering function, it hides, and it is reabsorbed by the urinary system and secreted back to plasma. Cellular metabolism is responsible for the continuous changes in the acid-base balance and is regulated by one or several of the systems that regulate the acid-base balance.

Until now, possible explanations have been proposed for the association between U-pH and diabetes. In this study incidence of diabetes and prediabetes was observed to increase in patients with urine PH 5. Furthermore, as PH progressed from 5 to 7, it was observed that the eGFR of the patients decreased and their levels of triglycerides and uric acid decreased.

U-pH is also low in people with a low or high body mass index. However, morbid obese patients were excluded in this study and their BMI values were not present.

Acid-base alterations are associated with insulin resistance, through defective renal ammoniagenesis and reduced insulin action in its signaling pathways (10,25,26). One of the possible explanations is the influence of insulin on renal excretion and ammoniac (NH4) production, which is an important urinary buffer (27). Insulin physiologically stimulates NH4 production and secretion. In the case of insulin resistance, this production and secretion of the proximal tubules is impaired (28). Metabolic acidosis increases cortisol secretion by stimulating glucocorticoid synthesis, increased cortisol production causes insulin resistance, and increased visceral obesity. Metabolic acidosis causes insulin resistance by affecting the levels of calcium and magnesium ions that are effective in insulin metabolism. In addition, the acidotic state disrupts insulin-like growth factor secretion, causing insulin ineffectiveness and hyperinsulinemia (14). Insulin level and insulin resistance were not evaluated in our study.

U-pH decreases due to increased excretion of hydrogen ions (H^+) into the urine or decreased elimination of urinary H^+ (29,30). Acceleration of the renin-angiotensin system and increased intrarenal oxidative stress lead to the supply of H^+ by activating the sodium-hydrogen exchanger (31–32). The supply of NH4 to urine controls, elimination of urinary H+, and lower plasma bicarbonate levels have been reported to pose a risk of incident diabetes (9,34). As U-pH correlates positively with body fluid pH, the U-pH level will be a surrogate marker of insulin resistance in the body.

A cohort study with 3119 men showed evidence that the risk of incident diabetes was significantly higher in men with the lowest U-pH (OR: 2.69; subjects with U-pH ≥6.5 as a reference) (20). In a population-based prospective study in 64660 Japanese adults, there was an association between dietary acid load score and type 2 T2DM in men, while in women it was not (19). Univariate and multivariate analysis showed that urine with low creatinine and triglyceride levels are risk factors for PH. In the univariate analysis, age, male gender, and hemoglobin were found to be associated with low U-pH levels. In many studies, low U-pH was found to be associated with obesity, diabetes, and insulin resistance in men, while the same was not found in women (35). U-pH in women has been reported to be higher than in men and this is associated with increased citrate excretion in the urine in women (35). In the same study, the risk of developing diabetes in male patients with low U-pH during a 10-year follow-up was approximately twice as high as in women. In this low rate of diabetes development in women, it is effective that estrogen increases hepatic gluconeogenesis and causes increased glucose entry into skeletal muscle (35,36).

Limitations

Despite the retrospective nature of this study, it also has several strengths, as it contains a large number of subjects. However, there are some acceptable limitations of our study. First, considering the literature showing that fasting U-pH is significantly correlated with 24-hour U-pH, we used spot urine testing to measure U-pH (38) Second, although individuals with a history of obesity in hospital records were excluded from the

study because U-pH was inversely correlated with body weight and body mass index, some individuals could not be separated due to a lack of body composition data (38). Third, although dietary components, the presence of acid-deficiency-related acidification defects, plasma pH, and plasma bicarbonate/lactate concentrations can affect U-pH, we did not have any data on them in our study (34,39,40). Fourth, the lack of electrolyte and ammonia measurements in the urine and, therefore, the urine base deficit could not be evaluated. Another limitation of our study was the lack of evaluation of liver function tests, family history of T2DM, smoking habits, and alcohol consumption. Therefore, more detailed prospective studies are needed.

CONCLUSION

In this study, the frequency of diabetes was found to be increased in patients with low U-pH. More detailed clinical studies are needed to evaluate whether different glucose tolerance statuses such as NGT, IFG, IGT, and T2DM are associated with U-pH.Financial Disclosure: No financial disclosure was declared by the authors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (Date: 08.07.2020, Decision No: 490).

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. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-53.
2. Ninomiya T, Perkovic V, De Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009; 20: 1813-21.
3. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: The Framingham Heart Study. Circulation 2007; 115: 1544-50.
4. Unwin N, Shaw J, Zimmet P, Alberti KGMM. Impaired glucose tolerance and impaired fasting glycaemia: The current status on definition and intervention. Diabet Med 2002; 19: 708-23.
5. Brannick B, Wynn A, Dagogo-Jack S. Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. Exp Biol Med (Maywood) 2016; 241: 1323-31.
6. Müller-Wieland PD med D, Nauck M, Petersmann A, et al. Definition, classification and diagnosis of diabetes mellitus. Exp Clin Endocrinol Diabetes 2019; 127: 1-7.
7. Siegelaar SE, Holleman F, Hoekstra JBL, DeVries JH. Glucose variability; does it matter? Endocr Rev 2010; 31: 171-82.
8. Poupin N, Calvez J, Lassale C, Chesneau C, Tomé D. Impact of the diet on net endogenous acid production and acid-base balance. Clin Nutr 2012; 31: 313-21.
9. Otsuki M, Kitamura T, Goya K, et al. Association of urine acidification with visceral obesity and the metabolic syndrome. Endocr J 2011; 58: 363-7.
10. Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K. Low urine pH: A novel feature of the metabolic syndrome. Clin J Am Soc Nephrol 2007; 2: 883-8.
11. Cameron MA, Maalouf NM, Adams-Huet B, Moe OW, Sakhaee K. Urine composition in type 2 diabetes: Predisposition to uric acid nephrolithiasis. J Am Soc Nephrol 2006; 17: 1422-8.
12. Hara S, Tsuji H, Ohmoto Y, et al. High serum uric acid level and low urine pH as predictors of metabolic syndrome: A retrospective cohort study in a Japanese urban population. Metabolism 2012; 61: 281-8.
13. Nakanishi N, Fukui M, Tanaka M, et al. Low urine pH is a predictor of chronic kidney disease. Kidney Blood Press Res 2012; 35: 77-81.
14. Marunaka Y. Roles of interstitial fluid pH in diabetes mellitus: Glycolysis and mitochondrial function. World J Diabetes 2015; 6: 125-35.
15. Aoi W, Hosogi S, Niisato N, et al. Improvement of insulin resistance, blood pressure and interstitial pH in early developmental stage of insulin resistance in OLETF rats by intake of propolis extracts. Biochem Biophys Res Commun 2013; 432: 650-3.
16. Zhang L, Curhan GC, Forman JP. Diet-dependent net acid load and risk of incident hypertension in United States women. Hypertension 2009; 54: 751-5.
17. Iwase H, Tanaka M, Kobayashi Y, et al. Lower vegetable protein intake and higher dietary acid load associated with lower carbohydrate intake are risk factors for metabolic syndrome in patients with type 2 diabetes: Post-hoc analysis of a cross-sectional study. J Diabetes Investig 2015; 6: 465-72.
18. Fagherazzi G, Vilier A, Bonnet F, et al. Dietary acid load and risk of type 2 diabetes: The E3N-EPIC cohort study. Diabetologia 2014; 57: 313-20.
19. Akter S, Kurotani K, Kashino I, et al. High dietary acid load score is associated with increased risk of type 2 diabetes in Japanese men: The Japan Public Health Center–based prospective study. J Nutr 2016; 146: 1076-83.
20. Hashimoto Y, Hamaguchi M, Nakanishi N, et al. Urinary pH is a predictor of diabetes in men; a population based large scale cohort study. Diabetes Res Clin Pract 2017; 130: 9-14.
21. Goel N, Calvert J. Understanding blood gases/acid-base balance. Paediatr. Child Health (Oxford) 2012; 22; 142-8;
22. Yucha C. Renal regulation of acid-base balance. Nephrol Nurs J 2004; 31: 201-6.
23. Clancy J, McVicar A. Short-term regulation of acid-base homeostasis of body fluids. Br. J. Nurs 2007; 16: 1016–21.
24. Adeva MM, Souto G. Diet-induced metabolic acidosis. Clin Nutr 2011; 30: 416-21.
25. Souto G, Donapetry C, Calviño J, Adeva MM. Metabolic acidosis-induced insulin resistance and cardiovascular risk. Metab Syndr Relat Disord 2011; 9: 247-53.
26. Hayata H, Miyazaki H, Niisato N, Yokoyama N, Marunaka Y. Lowered extracellular pH is involved in the pathogenesis of skeletal muscle insulin resistance. Biochem Biophys Res Commun 2014; 445: 170-4.

27. Klisic J, Hu MC, Nief V, et al. Insulin activates Na (+)/H (+) exchanger 3: biphasic response and glucocorticoid dependence. Am. J. Physiol. Renal Physiol 2002; 283: 532-9.
28. Yoshida S, Miyake T, Yamamoto S, et al. Relationship between urine pH and abnormal glucose tolerance in a community-based study. J Diabetes Investig 2018; 9: 769-75.
29. Ogawa S, Takiguchi J, Nako K, et al. Elucidation of the etiology and characteristics of pink urine in young healthy subjects. Clin Exp Nephrol 2015; 19: 822-9.
30. Ogawa S, Takiguchi J, Shimizu M, et al. The reduction in urinary glutamate excretion is responsible for lowering urinary pH in pink urine syndrome. Tohoku J Exp Med 2016; 239: 103-10.
31. Souma T, Abe M, Moriguchi T, et al. Luminal alkalinization attenuates proteinuria-induced oxidative damage in proximal tubular cells. J Am Soc Nephrol 2011; 22: 635-48.
32. Sato E, Mori T, Satoh M, et al. Urinary angiotensinogen excretion is associated with blood pressure in obese young adults. Clin Exp Hypertens 2016; 38: 203-8.
33. Ogawa S, Nako K, Okamura M, Ito S. Lower urinary pH is useful for predicting renovascular disorder onset in patients with diabetes. BMJ Open Diabetes Res Care 2015; 3: e000097.
34. Mandel EI, Curhan GC, Hu FB, Taylor EN. Plasma bicarbonate and risk of type 2 diabetes mellitus. CMAJ 2012; 184: 719-25.
35. Higashiura Y, Tanaka M, Furuhashi M, et al. Low urine pH predicts new onset of diabetes mellitus during a 10-year period in men: BOREAS-DM1 study. J Diabetes Investig 2020; 11: 1490-7.
36. Tramunt B, Smati S, Grandgeorge N, et al. Sex differences in metabolic regulation and diabetes susceptibility. Diabetologia 2020; 63: 453-61.
37. Capolongo G, Sakhaee K, Pak CYC, Maalouf NM. Fasting versus 24-h urine pH in the evaluation of nephrolithiasis. Urol Res 2011; 39: 367-72.
38. Taylor EN, Curhan GC. Body size and 24-hour urine composition. Am J Kidney Dis 2006; 48: 905-15.
39. Juraschek SP, Shantha GPS, Chu AY, et al. Lactate and risk of incident diabetes in a case-cohort of the atherosclerosis risk in communities (ARIC) study. PLoS One 2013; 8: e55113.
40. Kimura T, Hashimoto Y, Tanaka M, et al. Sodium-chloride difference and metabolic syndrome: A population-based large-scale cohort study. Intern Med 2016; 55: 3085-90.

Original Article

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Contribution of beverages to daily added sugar intake: compliance with guidelines' recommendations

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ABSTRACT

Aim: Beverages that contribute significantly to the daily added sugar intakes are reported to cause increased health problems such as obesity as long as their consumption is not limited. The aim of this study is to estimate added sugar intake from beverages.

Material and Method: This cross-sectional descriptive study conducted on 837 adults aged between 18-65 years. A questionnaire including questions about general socio-demographic characteristics (gender, occupation, income status, age, education) was applied. The beverage consumption within previous month was questioned using a beverage frequency questionnaire. The weight and height of the individuals were measured.

Results: In the present study, the mean added sugar intake from beverages was 13.1±17.6 g/day. Fruit drinks and caloric sodas had the highest contributions to daily added sugar intake, followed by sweetened tea and coffee. It was found that 11.95% and 9.68% of participants exceeded the recommendation of the American Heart Association and World Health Organization, respectively.

Conclusion: Sugar sweetened beverages are significant contributors to daily added sugar intake in Turkish population. Therefore, decreasing the consumption of sugar sweetened beverages should be main public health implementation to avoid the negative health outcomes including obesity, diabetes, cardiovascular diseases that may occur in the future.

Keywords: Added sugar, free sugar, sugar sweetened beverages, fruit drinks, caloric soda

INTRODUCTION

In recent years, the researchers focus on the intake of free sugars, especially in the form of sugar-sweetened beverages, that increase overall energy intake, may reduce the intake of more nutritionally foods and leading to an unhealthy diet, weight gain and increased risk of non-communicable diseases (1-3). Reduced intake of free sugars throughout the life course is recommended to provide health benefits (4). World Health Organization (WHO) recommends reducing the intake of free sugar below 10% of total energy. Additionally, the recommendation that reducing the intake of free sugars below 5% of total energy intake would provide additional health benefits was determined as conditional (5). WHO uses the term of "free sugar" while developing the recommendation, whereas the American Heart Association (AHA) uses the term of "added sugar". The AHA recommends added sugar no more than 25 grams for females and 37 grams for males (6). The terms of free sugar and added sugar are actually quite similar to each other. The difference in the term of free sugar is the inclusion of sugar, which is naturally found in fruit juices and fruit juice concentrates (5,7). Both terms are frequently used in studies assessing the compliance of sugar consumption amounts with the recommendation (8-10). In one of these studies, the median free sugar and added sugar intake are 14% (74 g/day) and 12% (64 g/day) of total energy, respectively. Non-alcoholic beverages especially soft drinks are the main sources of free and added sugars in adults (8). Similarly, beverages contribute most (47%) to added sugar in American diets according to NHANES data (11). Added sugar intake is about 16.3% of total energy in United States (12). In Canada, the mean added sugar intake is 11-13% of total energy. The main contributor of added sugar intake is soft drinks

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(13). Therefore, it is mentioned that the consumption of sugar sweetened beverages as "probable contributor" to the increased prevalence of obesity is worth to investigate given the high contribution of soft drinks and the amounts of discretionary beverages including sugar sweetened beverages in diet (14,15). It is important to note that The Heart and Stroke Foundation of Canada declares the free sugar intake should be less than 10% of total energy by assessing the sugar sweetened beverage consumption patterns obtained from prospective cohort studies in accordance with WHO (16).

In this context, this study aims (1) to estimate added sugar intake from beverages in adults; (2) to describe beverage types which are the main sources of added sugar; (3) to investigate the association of added sugars with demographic descriptors; and (4) to determine the adherence to the recommendations for added sugar.

MATERIAL AND METHOD

Study Design, Participants and Recruitment

This cross-sectional descriptive study conducted between June 2019 and October 2019 on 837 adults aged between 18-65 years. The study was carried out in randomly selected individuals living in Ankara, the capital city of Turkey. The individuals who had chronic disease, pregnant and lactating ones were excluded. Consents of the participants were obtained through the voluntary consent form in accordance with the Helsinki declaration. This study was approved by Gazi University Ethics Committee (Date: 14.11.2017, Decision No: 2017439). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A questionnaire including questions about general socio-demographic characteristics (gender, occupation, income status, age, education), the frequency of beverage consumption were applied via face to face interview. The weight (kg; with calibrated device) and height (cm; with portable stadiometer) of the individuals were measured by the researchers to nearest 0.5 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as the weight (kg) divided by the squared of height (m^2). The BMI values were classified into three categories: underweight (<18.5 kg/m^2), normal or healthy weight (18.5-24.9 kg/m^2), and overweight or obese (≥25.0 kg/m^2) (17).

Instruments, Measures, and Procedures

The beverage consumption within previous month was questioned using a beverage frequency questionnaire which was applied in similar researches (18-20) and adapted to Turkish by the researchers. Frequency categories were responded on never, daily, weekly or monthly basis and then the amount or serving size of each beverage reported was asked. Name brands of the beverages consumed were also provided to determine the added sugar intake more reliably. Frequency ("How often") is converted to the unit of times per day, then multiplied by the amount consumed ("How much each time") to provide average daily beverage consumption in mL per day.

Added sugars in the mean amount of beverages consumed per day were calculated by modeling the methods of Louie et al. (21) 2015. The adapted method to calculate added sugar in the beverages is presented in the **Figure 1**. Gray box indicates decision end points. When information of the added sugar content was limited similar to Step 5 in **Figure 1**, the added sugar was calculated as sugar content of the beverage minus natural occurring sugar estimated by comparison with unsweetened variety by modeling the methods of Sluik et al. (8) 2016 . In this step, different method was used from Louie et al. (21) 2015. However, similar results were obtained. In the present study, the steps up to Step 5 in **Figure 1** were sufficient for the added sugar calculation. There was no need to use Step 6 in **Figure 1**.

Free sugars were calculated by collecting added sugars with the sugars naturally present in fruits juices and fruit concentrates. The prevalence of excessive added sugar intake from beverages was assessed using the AHA's recommendation (25 grams for females and 37 grams for males). Total energy requirement was used to calculate how much percentage of the daily energy met from free sugar in the beverages according to the free sugar intake recommendation of WHO (below 10% of total energy). The equations proposed by Schofield in 1985 were selected according to the age and gender of the participants to calculate basal metabolic rate (22); then multiplied it by the corresponding physical activity level depending on their occupation to estimate the individuals' energy requirements (23).

Data Analysis

The data were evaluated using SPSS 22.0 statistic package program software. Mean and standard deviation were obtained using descriptive statistics. The data providing parametric condition was evaluated using independent sample t test to describe the mean differences and significance. Chi-square test was used to predict the differences between categorical parameters. The findings were determined within a 95% confidence interval and in the $p<0.01$ and $p<0.05$ significance level. The participants met the recommendations was presented using percentages. The compliance two different recommendations for added sugar intake in making the distinction by evaluating the participants as excess sugar intake and recommended level of sugar intake was assessed using the kappa test.

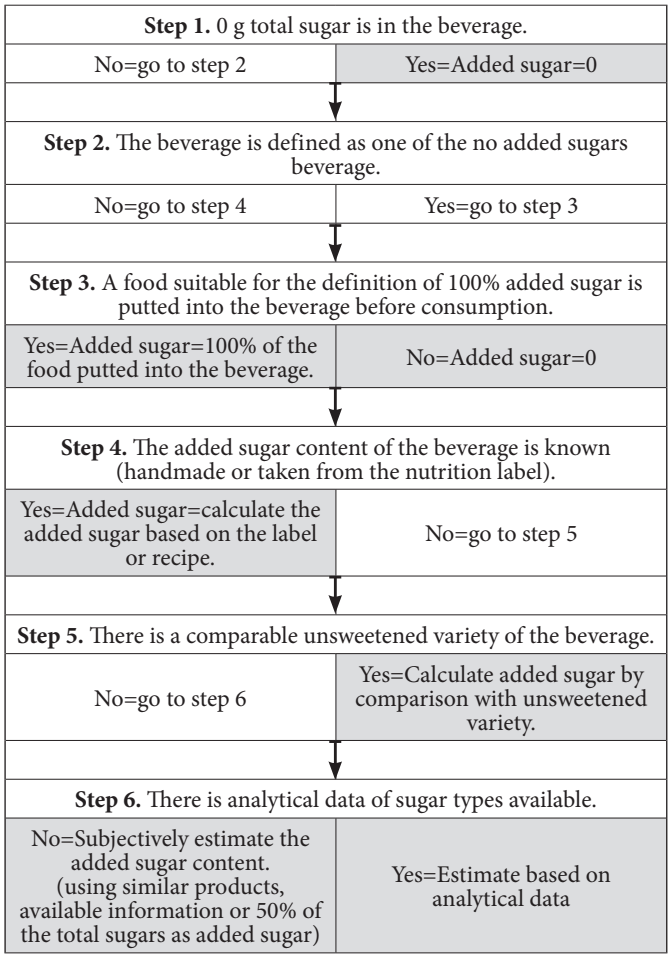

Figure 1. Flow diagram adapted from Louie et al., 2015 for assessment added sugar in beverages (21).

RESULTS

Demographic Descriptors, Sugar Sweetened Beverages Consumption and Added Sugar Intake

The demographic descriptors, sugar sweetened beverage consumption and the mean added sugar intake from beverages of the participants were presented in **Table 1**. The mean amounts of sugar sweetened beverage (SSB) consumption and added sugar intake from beverages was 232.5±327.7 mL/day and 13.1±17.6 g/d, respectively. In general, males had higher the daily consumption of SSB, added sugar intake from beverages than females ($p < 0.001$). According to age groups, the amounts of SSB consumption and added sugar intake from beverages were higher in older participants (18-30 years) than the other age group (31-65 years) ($p < 0.001$; $p<0.05$, respectively). Although in low socioeconomic level, both the amounts of SSB consumption (267.8±311.7 mL/day) and added sugar intake from beverages (15.4±22.1 g/day) were higher than the other socioeconomic levels, the difference was not statistically significant ($p>0.05$). Individuals with higher education level consumed more SSB than in that of lower education level even though not statistically significant. Added sugar intake from beverages of the individuals at higher education level was more, significantly ($p<0.001$). According to BMI, overweight and obese were found to consume more SSB and added sugar ($p>0.05$). The differences among the BMI categories were not significant ($p>0.05$).

Table 1. Demographic descriptors, sugar sweetened beverages consumption and added sugar intake from beverages of participants

Characteristics	n (%)	SSB (Mean±SD, mL)	Added Sugar (Mean±SD, g)
Total participants	837 (100)	232.5±327.7	13.1±17.6
Gender			
Males	191 (22.8)	340.8±449.6**	18.9±25.4**
Females	646 (77.2)	200.5±274.1	11.3±14.0
Age (Years)			
18-30	757 (90.4)	221.9±305.2	12.5±15.1
31-65	80 (9.6)	332.4±483.8**	18.1±32.5*
Socioeconomic level			
Low	220 (26.3)	267.8±311.7	15.4±22.1
Medium	541 (64.6)	214.9±323.6	12.1±15.7
High	76 (9.1)	255.9±390.7	13.5±15.1
Education			
≤ 8 years	50 (6.0)	189.9±320.1	8.1±12.6
> 8 years	787 (94.0)	235.2±328.2	13.3±17.8**
BMI (kg/m²)			
Underweight	99 (11.8)	216.5±267.4	13.3±16.5
Normal weight	551 (65.8)	234.9±335.9	12.8±15.6
Overweight and obese	187 (22.4)	234.0±333.3	13.6±22.9

*p < 0.05; ** p < 0.001; BMI, body mass index; SD, standard deviation; SSB, sugar sweetened beverages.

Daily Energy and Added Sugar Intake from Beverages

Mean daily energy and added sugar intake from beverages according to all participants and to only consumers were presented in **Table 2**. Plain milk was preferred to sweetened milk beverages by 96.3% of the participants. The mean percentage of the participants consumed 100% fruit juice was 34.4% while 43.8% preferred to consume fruit drinks. The mean percentages of individuals who consumed sweetened coffee and tea, and caloric soda was found 49.5% and 56.0%, respectively.

The beverages with the highest consumption amounts were unsweetened tea and coffee (281.4±379.8 mL/day), plain milk (160.6±193.4 mL/day) and sweetened tea and coffee (153.9±285.6 mL/day) according to mean consumption of all participants, respectively. On the other hand, unsweetened tea and coffee (430.6±395.6 mL/day), sweetened tea and coffee (311.1±340.7 mL/day), plain milk (166.7±194.4 mL/day) and low caloric soda (160.5±327.1 mL/day) were the beverages with highest consumption according to only consumers. Plain milk contributed ~79.5 kcal to the diet. Caloric soda was the beverage providing the second highest level energy; ~25.4 kcal came from caloric soda which had the

most contribution compared to other sugar sweetened beverages according to all participants. Additionally, when examining the mean energy intake in only consumers, all of the sugar sweetened beverages were determined to contribute to energy with similar averages excluding beverages contain naturally occurred sugar such as plain milk and sweetened milk beverages.

Contribution of added sugar to total energy requirement was ~1% in consumers. Caloric soda contributed the most energy to total energy requirement with the percentage of 1.8%.

In **Figure 2**, the assessment was based on the added sugar and free sugar received from the beverages only. Although the assessment only included the sugar from beverages, 11.95% and 9.68% of participants exceeded the recommendation of AHA and WHO, respectively.

The majority of the participants (88.05% and 90.32%) were found not to exceed the recommendation of AHA and WHO, respectively (**Figure 2**). According to the kappa statistical results, the agreement between the recommendations of WHO and AHA was significant ($p < 0.001$, **Figure 2**), and the agreement rate was 87.0% between them.

DISCUSSION

In the present study, the mean added sugar intake from beverages was 13.1±17.6 g/day. Males, individuals aged between 31-65 years and at the higher education level had the highest added sugar intake from beverages. Fruit drinks and caloric sodas had the highest contributions from added sugars to total energy requirements, followed by sweetened tea and coffee.

Thompson et al., 2009 were found males to have higher added sugar intake than females according to the NHANES 2003-2004 data, similar to the results of present study. In another study, the added sugar intake of males was higher than females (10), similarly. On the other hand, the youngest age group had higher added sugar intake (10), unlike the present study.

The mean amounts of added sugar intakes were 52 g in Canadian adults (13), 77 g in US adults (23), 64 g in Dutch adults per day (8). Direct comparisons of the present study with other studies are difficult not only because of the assessment of added sugar intake from only beverages in this study, but also because of the variability in definitions. Added sugar definition was used more frequently in the studies (1, 7, 13, 14, 24-26) while in others, free sugar definition was evaluated (8-10).

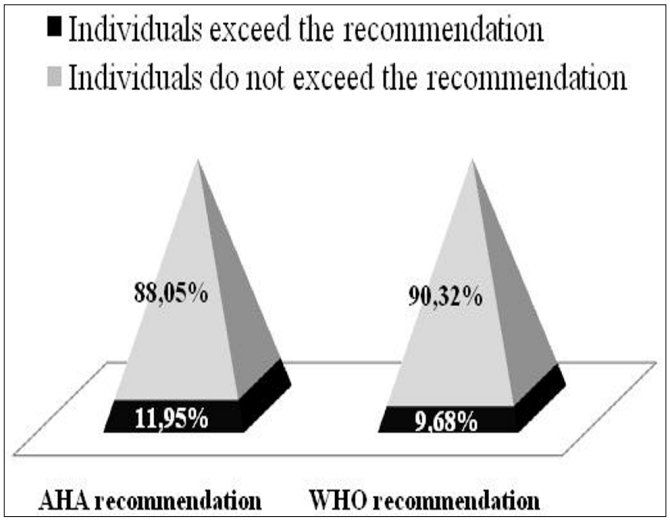

Figure 2. Comparison of added sugar and free sugar intakes of individuals with AHA and WHO recommendations.

Table 2. Daily energy and added sugar intake from beverages

Beverages	Consumers n(%)	Amount of beverages (Mean±SD, mL/d)		Energy intake (Mean±SD, kcal/d)		Added sugar intake (Mean±SD, g/d)		Contribution of added sugar to total energy requirement (Mean±SD, %)	
		Total	Consumers	Total	Consumers	Total	Consumers	Total	Consumers
Water	836 (99.8)	1518.1±670.2	1519.9±668.6	-	-	-	-	-	-
Milk									
Sweetened milk beverages	44 (5.3)	1.9±35.0	37.5±150.2	4.1±73.7	78.7±315.5	0.3±2.1	5.1±7.9	0.04±0.3	0.7±0.9
Plain milk	806 (96.3)	160.6±193.4	166.7±194.4	79.5±90.5	82.6±90.1	-	-	-	-
Fruit beverages									
%100 fruit juices	288 (34.4)	22.0±75.8	63.9±118.6	10.1±34.9	29.4±54.6	-	-	-	-
Fruit drinks	367 (43.8)	32.7±85.2	74.5±116.1	16.3±42.6	37.2±58.0	3.6±9.4	8.2±12.8	0.6±1.5	1.5±2.1
Tea and coffee									
Sweetened tea and coffee	414 (49.5)	153.9±285.6	311.1±340.7	15.4±28.5	31.1±34.1	3.8±7.1	7.8±8.5	0.7±1.1	1.3±1.4
Unsweetened tea and coffee	547 (65.4)	281.4±379.8	430.6±395.6	2.7±4.2	4.1±4.7	-	-	-	-
Soda									
Caloric	469 (56.0)	42.4±110.6	75.6±139.1	25.4±66.4	45.4±83.4	4.4±11.4	7.8±14.3	1.1±2.3	1.8±2.9
Low calorie	28 (3.3)	5.4±65.5	160.5±327.1	1.0±13.0	32.1±65.4	-	-	-	-
Alcoholic beverages	129 (15.4)	13.7±73.0	88.9±167.5	6.8±35.8	45.1±82.2	-	-	-	-
Sports and energy drinks	59 (7.0)	1.8±10.4	25.4±30.6	0.7±4.1	10.1±12.2	0.2±1.2	2.9±3.6	0.03±0.2	0.4±0.5

SD, standard deviation.

The mean intake of added sugars did not exceed the recommendations. However, consumers who exceeded the recommendation of AHA and WHO constituted one-tenth of all participants despite considering the added sugars the only from beverages. This rate is thought to be only the tip of the iceberg; such a finding was obtained although amounts of added sugar were assessed from only beverages. In New Zealand, 58% of adults exceeded this recommendation (10). In study conducted by Sluik et al. (8), 2016, 29-33% of the adults adhered to the WHO recommendation. In another study in 4140 Australian children and adolescents, 18% of the participants were consistent with the WHO recommendation (25). Studies examined the compliance of added sugar intake with the recommendation is very limited. In the present study, according to added sugar intake from beverages, 11.95% and 9.68% of participants exceeded the recommendation of AHA and WHO, respectively. In Turkey, the study evaluating added and free sugar intakes has not been conducted yet according to our present knowledge. If dietary intakes of individuals are assessed, this ratio is likely to be higher. On the other hand, many studies evaluated the effects of added sugar on health with evidences of sugar sweetened beverages consumption (27-29). Moreover, the authorities including The Heart and Stroke Foundation of Canada and United States Department of Agriculture (16,17) developed recommendations for added sugar intake based on studies assessing the sugar sweetened beverage consumption of populations (27-30). Similarly, in studies assessed the added sugar intake has found that sugar sweetened beverages were the main contributors to added sugar intake (8,14). Therefore, the percentages and amounts of added sugar intake obtained from this study is thought to reflect the consumption of the population. Additionally, SSB is determined as a suitable indicator to develop public health policy because SSB is one of the causes of obesity and empty calorie source (15,31). This health effect was shown in many prospective cohort studies, weight gain and obesity had association with SSB consumption (32-34). However, in this study, there was no difference in the amounts of added sugar intake between BMI groups.

In this study, the main contributor of added sugar intake was caloric soda, followed by fruits drinks and sugar sweetened tea and coffee. The consumption of sugar-free tea or coffee instead of sugar sweetened beverages has positive health effects. In cohort studies, tea and coffee was determined to have associations with lower risk of cardiovascular disease and type 2 diabetes (34,35). Additionally, 100% fruit juices are healthy alternatives to fruit drinks provided that 4-6 oz (~118.3-177.4 mL) does not exceed (31). The consumption of diet soda instead of caloric soda affect health more positively (36,37), but it is also stated that it should be approached cautiously (31).

Limitations

First one of the limitations of this study was the beverages consumption was assessed according to a non-validated questionnaire instead of 24 h dietary recall. Secondly, the added sugar intake from overall diet was not calculated because of the previous limitation. Thirdly, as in all added sugar studies, obtaining the added sugar contain of some beverages was difficult. Despite the study limitations, it is worth to mention that this is the first study to assess the added sugar intakes among Turkish adults.

CONCLUSION

The results of this study support the evidence that sugar sweetened beverages are significant contributors to added sugar intake. Added sugar intake from beverages was higher than the recommended levels in 10% of the participants. Studies should be conducted to provide further support to limit consumption of these beverages in place of healthy alternatives such as water to reduce obesity-related chronic disease risk in Turkish population.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Gazi University Ethics Committee (Date: 14.11.2017, Decision No: 2017439).

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(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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REFERENCES

1. Lula EC, Ribeiro CC, Hugo FN, Alves CM, Silva AA. Added sugars and periodontal disease in young adults: an analysis of NHANES III data. Am J Clin Nutr 2014; 100: 1182-7.
2. Te Morenga LA, Howatson AJ, Jones RM, Mann J. Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. Am J Clin Nutr 2014; 100: 65-79.
3. Singh GM, Micha R, Khatibzadeh S, et al. Estimated Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Estimated global, regional, and national disease burdens related to sugar-sweetened beverage consumption in 2010. Circulation 2015; 132: 639-66.

4. World Health Organization. Information note about intake of sugars recommended in the WHO guideline for adults and children. Geneva, Switzerland: WHO Document Production Services; 2015a.
5. https://www.who.int/nutrition/publications/guidelines/sugar_intake_information_note_en.pdf Accessed May 15, 2021.
6. World Health Organization. Guideline: Sugars intake for adults and children. ISBN: 9789241549028. Geneva, Switzerland: WHO Document Production Services; 2015b. Accessed April 30, 2021.
7. The American Heart Association. Dietary sugars intake and cardiovascular health a scientific statement from the American Heart Association. Circulation 2009; 120: 1011-20.
8. Erickson J, Slavin J. Are restrictive guidelines for added sugars science based? Nutrition 2015; 14: 124.
9. Sluik D, van Lee L, Engelen AI, Feskens EJ. Total, free, and added sugar consumption and adherence to guidelines: the Dutch National Food Consumption Survey 2007-2010. Nutrients 2016; 8: 70.
10. Mok A, Ahmad R, Rangan A, Louie JCY. Intake of free sugars and micronutrient dilution in Australian adults. Am J Clin Nutr 2018; 107: 94-104.
11. Kibblewhite R, Nettleton A, McLean R, et al. Estimating free and added sugar intakes in New Zealand. Nutrients 2017; 9: 1292.
12. United States Department of Agriculture (USDA). Scientific Report of the 2015 Dietary Guidelines Advisory Committee. https://health.gov/dietaryguidelines/2015-scientific-report/pdfs/scientific-report-of-the-2015-dietary-guidelines-advisory-committee.pdf Accessed May 10, 2021.
13. Newens KJ, Walton J. A review of sugar consumption from nationally representative dietary surveys across the world. J Hum Nutr Diet 2016; 29: 225-40.
14. Brisbois TD, Marsden SL, Anderson GH, Sievenpiper JL. Estimated intakes and sources of total and added sugars in the Canadian diet. Nutrients 2014; 6: 1899-912.
15. Sanchez-Pimienta TG, Batis C, Lutter CK, Rivera JA. Sugar-sweetened beverages are the main sources of added sugar intake in the Mexican population. J Nutr 2016; 146: 1888–96.
16. World Health Organization/Food and Agriculture Organization. Diet, nutrition and the prevention of chronic diseases—report of a Joint WHO/FAO Expert Consultation. Geneva: World Health Organization; 2003.
17. http://apps.who.int/iris/bitstream/handle/10665/42665/ WHO_TRS_916.pdf?sequence=1 Accessed April 30, 2021.
18. The Heart and Stroke Foundation of Canada (HSFC). Position Statement : Sugar, heart disease and stroke; 2014. Accessed April 25, 2021.
19. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363: 157–63.
20. West DS, Bursac Z, Quimby D, et al. Self-reported sugar-sweetened beverage intake among college students. Obesity 2006; 14: 1825-31.
21. Berkey CS, Rockett HRH, Field AE, Gillman MW, Colditz GA. Sugar-added beverages and adolescent weight change. Obes Res 2004; 12: 778-88.
22. Opoku-Acheampong AA, Kidd T, Adhikari K, Muturi N, Kattelmann K. Assessing physical activity, fruit, vegetable, and sugar-sweetened beverage intake patterns of college students in Kansas. J Nutr Educ Behav 2018; 50: 977-83.
23. Louie JCY, Moshtaghian H, Boylan S, et al. A systematic methodology to estimate added sugar content of foods. Eur J Clin Nutr 2015; 69: 154–61.
24. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985; 39C: 5–41.
25. WHO. Energy and protein requirements: Report of a joint FAO/WHO/UNU expert consultation. WHO Technical Report Series No. 724. Geneva; 1985. http://www.fao.org/3/a-y5686e.pdf Accessed October 18, 2020.
26. Ervin RB, Ogden CL. Consumption of added sugar among U.S. adults, 2005–2010. NCHS Data Brief 2013; 122: 1–8.
27. Louie JCY, Moshtaghian H, Rangan AM, Flood VM, Gill TP. Intake and sources of added sugars among Australian children and adolescents. Eur J Nutr 2016; 55: 2347-55.
28. Thompson FE, McNeel TS, Dowling EC, et al. Interrelationships of added sugars intake, socioeconomic status, and race/ ethnicity in adults in the United States: National Health Interview Survey, 2005. J Am Diet Assoc 2009; 109: 1376-83.
29. Singh GM, Micha R, Katibzadeh S, et al. Mortality due to sugar sweetened beverage consumption: A global, regional and national comparative risk assessment. Circulation 2018; 127: AMP22.
30. Buhler S, Raine KD, Arango M, Pellerin S, Neary NE. Building a strategy for obesity prevention one piece at a time: The case of sugar-sweetened beverage taxation. Can J Diabete 2013; 37: 97-102.
31. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar sweetened beverages, obesity, type 2 diabetes mellitus and cardiovascular disease risk. Circulation 2010; 121: 1356-64.
32. Kristal RB, Blank AE, Wylie-Rosett J, Selwyn PA. Factors associated with daily consumption of sugar-sweetened beverages among adult patients at four federally qualified health centers, Bronx, New York, 2013. Prev Chronic Dis 2015; 12: E02.
33. Hu FB. Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. Obes Rev 2013; 14: 606–19.
34. Lim L, Banwell C, Bain C, et al. Sugar sweetened beverages and weight gain over 4 years in a Thai national cohort—a prospective analysis. PLoS One 2014; 9: e95309.
35. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011; 364: 2392–2404.
36. O'Connor L, Imamura F, Lentjes MA, et al. Prospective associations and population impact of sweet beverage intake and type 2 diabetes, and effects of substitutions with alternative beverages. Diabetologia 2015; 58: 1474-83.
37. Bhupathiraju SN, Pan A, Manson JE, et al. Changes in coffee intake and subsequent risk of type 2 diabetes: three large cohorts of US men and women. Diabetologia 2014; 57: 1346-54.
38. Ma J, Jacques PF, Meigs JB, et al. Sugar-sweetened beverage but not diet soda consumption is positively associated with progression of insulin resistance and prediabetes. J Nutr 2016; 146: 2544-50.
39. Carwile JL, Willett WC, Spiegelman D, et al. Sugar-sweetened beverage consumption and age at menarche in a prospective study of US girls. Hum Reprod 2015; 30: 675-83.

Original Article

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Factors affecting occupational burnout in nurses working in a medical oncology clinic

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ABSTRACT

Objective: To reveal the factors that may affect the burnout level of nurses working in a medical oncology clinic.

Material and Method: This study was a cross-sectional observational descriptive study conducted in a medical oncology clinic. The study included 29 female nurses who were currently working in a medical oncology clinic. Participants were assessed with sociodemographic information form and Turkish versions of the occupational fatigue exhaustion/recovery scale (OFER), the professional quality of life (ProQOL) scale, and the Beck depression inventory (BDI). Participants with a low burnout score and a high burnout score were identified as group A and group B and were compared about factors that could affect burnout.

Results: Group A and group B were similar in terms of sociodemographic parameters. OFER-chronic fatigue subscale median (IQR) scores for Group A and Group B were 43.0 (33.00-58.50) and 63.0 (50.0-83.0), respectively (p = 0.032). OFER-inter-shift fatigue subscale median (IQR) scores for Group A and Group B were 50.0 (37.00-57.75) and 37.0 (20.00-43.00), respectively (p = 0.005). Median scores of OFER-acute fatigue, ProQOL compassion satisfaction, and compassion fatigue, and BDI were similar between groups. In binary logistic regression analysis, the odds ratios of OFER-chronic fatigue and OFER-inter-shift fatigue were 1.027 (95% CI 0.980-1.077, p=0.263) and 0.904 (95% CI 0.828-0.988, p=0.025), respectively.

Conclusion: Our study revealed that the most crucial factor related to the occupational burnout of nurses might be inter-shift fatigue (recovery). Interventions to target inter-shift fatigue could potentially protect nurses from burnout.

Keywords: Occupational burnout, oncology nurses, occupational fatigue exhaustion/recovery scale, professional quality of life scale, Beck depression inventory, inter-shift fatigue

INTRODUCTION

Cancer is a challenging disease for both patients and healthcare professionals. Nurses who are at the forefront in the care of cancer patients experience many physical and psychological difficulties (1,2). Helping people exposed to traumatic stressors have been associated with burnout and depression (3). A recent meta-analysis shows that ten percent of nurses worldwide have high burnout symptoms (4). Evidence indicates that oncology nurses are particularly vulnerable to occupational stress, and this can affect nurses' professional quality of life (5,6). Nurses' compassion satisfaction, burnout level, and compassion fatigue are important concepts affecting the quality of nursing care given to patients (7). Moreover, decreasing the level of burnout is associated with better patient care and patient satisfaction (8).

Compassion fatigue occurs when the caregiver cannot shield or save the individual from harm and results in feelings of guilt and distress (3,9). The levels of compassion fatigue and burnout, which are the most frequently reported work-related consequences for nurses, are particularly high for oncology nurses (10-12). Quality of care, nurses' performance, patients' outcomes, nurses' safety, and quality of communications with colleagues and patients can be negatively affected by a high level of compassion fatigue (13).

Characterized by hopelessness, reduced energy and strength, frustration, anger, and depression, burnout is often associated with a very high workload or an unsupportive work environment (3). Especially; healthcare professionals are among the riskiest job

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groups in terms of burnout (9,14). Increased burnout levels and decreased job satisfaction in healthcare professionals negatively affect the employees' quality of life and impair nursing care and services quality (9,14).

Occupational fatigue is defined as mental or physical fatigue that prevents a person from functioning normally due to prolonged physical and/or mental exertion without sufficient time to rest and recover (15). Long working hours, multiple-night shifts, and insufficient rest between shifts are also associated with higher nurse fatigue (16). Occupational fatigue can be divided into three different types as acute fatigue, chronic fatigue, and inter-shift (recovery) fatigue (17). Acute occupational fatigue is defined as a feeling of lack of energy as a direct consequence of previous work activities (18). Chronic occupation fatigue results from high levels of acute fatigue in addition to insufficient recovery between work shifts which persists even on rest days (19). Chronic fatigue is correlated with more negative consequences on workers' health, well-being, and work performance than acute fatigue (20). The third type is recovery compassion fatigue that exists when nurses do not feel recovered from a previous shift at the start of the next shift (21). In studies, fatigue, especially in nurses returning shifts, was associated with poor job performance needle bars, musculoskeletal injuries, obesity, and depression (22,23).

In this study, we aimed to reveal the factors that may affect the burnout level of nurses working in a medical oncology clinic.

MATERIAL AND METHOD

This study was a cross-sectional observational descriptive study conducted in the medical oncology clinic of a tertiary referral center. Nurses who did not have a physical or mental disability preventing them from understanding what they read and filling out questionnaires, who agreed to participate in the study, and who were currently working in the medical oncology clinic were included in the study. Sociodemographic information form and Turkish versions of the occupational fatigue exhaustion/recovery scale (OFER), the professional quality of life (ProQOL) scale, and the Beck depression inventory (BDI) were given to the nurses in print, and the participants were asked to complete them themselves. The study was conducted after the approval of the Ankara Onkoloji Training and Research Hospital Clinical Researchs Ethics Committe (Date: 21.04.2021, Decision No: 2021-04/1128). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Sociodemographic Information Form

A constructed demographic information form included questions about age, working time in the medical oncology clinic, marital status (single or married), living alone or with other family members, comorbidities (i.e. diseases such as hypertension, diabetes mellitus, osteoarthritis, migraine), income level (what participants report as low, medium, or high, in their own opinion), exposure to verbal or physical violence at work, whether she likes her job or not, feeling of strain and history of psychiatric disorder and treatment.

Occupational Fatigue Exhaustion/Recovery Scale

Winwood et al. (20) developed the occupational fatigue exhaustion/recovery scale to measure occupational fatigue. The scale consists of 15 items and includes three sub-dimensions: chronic fatigue, acute fatigue, and inter-shift fatigue (recovery). For scale responses, a 7-point Likert type scale with 6 points (0=Strongly Disagree, 1=Disagree, 2=Somewhat Disagree, 3=Neither Agree nor Disagree, 4=Somewhat Agree, 5=Agree, 6=Strongly Agree) is used. The scale does not have a total score, and it is calculated separately for each sub-dimension (item-total scores/30 ×100). A score between 0 and 100 is obtained for each sub-dimension. For the sub-dimensions chronic fatigue and acute fatigue, scoring 0-25 shows low fatigue, 25-50 medium/low fatigue, 50-75 medium/high fatigue, and 75-100 shows high fatigue. A high score in the inter-shift fatigue (recovery) sub-dimension indicates that there is recovery between shifts (24). In the validity and reliability studies conducted by Havlioğlu et al. (25) for the Turkish version of the scale, the Cronbach's alpha coefficient was 0.85 in the chronic fatigue sub-dimension, which was 0.67 in acute fatigue sub-dimension, and 0.68 in the recovery sub-dimension.

Professional Quality of Life Scale, Version 5

The ProQOL is a 30-item self-report measure composed by three subscales (3). The first subscale measures compassion satisfaction, defined as the “pleasure derived from being able to do one's work (helping others) well” (10 items). Higher scores on this scale represent greater satisfaction. The second subscale measures burnout, defined as “feelings of hopelessness and difficulties in dealing with work or in doing one's job effectively” (10 items). The third subscale measures secondary traumatic stress, defined as “work-related, secondary exposure to people who have experienced extremely or traumatically stressful events” (10 items). Considering that the terms "compassion fatigue" and "secondary traumatic stress" are used interchangeably in the literature, we will use the term “compassion fatigue” to refer to this factor. Higher scores from these two subscales indicate higher levels of burnout and compassion fatigue, respectively. Respondents are instructed to indicate how frequently each item was experienced in the previous 30 days on a

5-item Likert scale (from 1=never to 5=very often). The score that can be obtained from each subscale varies between 0 and 50 (3). In the study for the reliability of the Turkish version of scale conducted by Yeşil et al, the Cronbach's alpha value of ProQOL was 0.848, and the Cronbach's alpha values of compassion satisfaction, burnout, and compassion fatigue subscales were 0.884, 0.575 and 0.841, respectively (26).

Beck Depression Inventory

The Beck depression inventory consists of 21 questions, each of which scores between 0 and 3 (27). High scores on this scale indicate an increase in the severity of depressive complaints (27). Hisli et al. (28) demonstrated the validity and reliability of the Turkish version of the BDI with a Cronbach alpha coefficient of 0.80.

Statistical Analysis

Statistical analysis was performed using SPSS software (SPSS for Windows, version 24.0., SPSS Inc., Chicago, USA). Numeric data were presented as median (interquartile range-IQR), and categorical data were presented as frequency (percentage). The participants were divided into two subgroups according to ProQOL-burnout subscale scores. Participants with a low burnout score (ProQOL-burnout subscale score lower than median) and a high burnout score (ProQOL-burnout subscale score higher than median) were identified as group A, and group B. Group A and group B were compared by using Pearson's chi-square test and Mann-Whitney U test for categorical data and nonparametric numerical data, respectively. Multivariate logistic regression analysis was performed using variables with a p-value below 0.05 due to univariate analysis to determine independent factors predicting high ProQOL-burnout subscale scores. All statistical tests were two-sided, and p-values of <0.05 were considered statistically significant.

RESULTS

Study Population

The study included 29 female nurses with a median age of 28.0 (IQR, 24.5-41.0) and currently working in a medical oncology clinic. Seventeen (58%) of the participants worked in the medical oncology clinic for at least three years, and 19 (65.5) were on night shifts. Eleven (37.9%) nurses were single, 18 (62.1%) were married, and six (20.7%) nurses were living alone. Eighteen (62.1%) participants had children. Eighteen (62.1%) and 11 (37.9%) participants stated their income levels as moderate and high, respectively. Seven (24.1%) participants had comorbidities, and only one of them (3.4%) was receiving psychiatric treatment for depression. Thirteen (44.8%) nurses were subjected to verbal or physical violence while doing their job. The number of nurses who had difficulties while doing their job and who had no job satisfaction were 19 (65.5%) and three (10.3%), respectively. Median OFER chronic fatigue, acute fatigue, and inter-shift (recovery) fatigue subscale scores were 57.0 (IQR, 40.0-70.0), 73.0 (IQR, 63.0-80.0), and 43.0 (IQR, 33.0-53.0), respectively. Median ProQOL compassion satisfaction, burnout, and compassion fatigue subscale scores were 31.0 (IQR, 26.0-38.5), 19.0 (IQR, 16.0-25.0), and 19.0 (IQR, 12.0-26.5), respectively. Median BDI score was 11.0 (IQR, 4.0-19.5).

Comparison of Groups Formed According to Burnout Level

Twenty-nine participants were divided into two groups: those with ProQOL-burnout scores less than median (Group A, n=14) and those with equal or greater than median (Group B, n=15). Both groups were similar in terms of main sociodemographic parameters (**Table 1**).

Table 1. Comparison of Group A and Group B in terms of main sociodemographic parameters

Parameter	Group A (n=14)	Group B (n=15)	p-value
Age, median (IQR)	33.0 (27.75-41.50)	25.0 (24.00-36.00)	0.130
Working time			0.264
<3 years	4 (28.6)	8 (53.3)	
≥3 years	10 (71.4)	7 (46.7)	
Marital status			0.128
Single	3 (21.4)	8 (53.3)	
Married	11 (78.6)	7 (46.7)	
Lives alone			0.169
No	13 (92.9)	10 (66.7)	
Yes	1 (7.1)	5 (33.3)	
Have a child			0.450
No	4 (28.6)	7 (46.7)	
Yes	10 (71.4)	8 (53.3)	
Night shift			0.700
No	4 (28.6)	6 (40.0)	
Yes	10 (71.4)	9 (60.0)	
Income status			0.710
Moderate	8 (57.1)	10 (66.7)	
High	6 (42.9)	5 (33.3)	
Comorbidity			0.215
No	9 (64.3)	13 (86.7)	
Yes	5 (35.7)	2 (13.3)	
Feeling strained			
No	5 (35.7)	5 (33.3)	1.000
Yes	9 (64.3)	10 (66.7)	
Exposure to violence			0.715
No	7 (50.0)	9 (60.0)	
Yes	7 (50.0)	6 (40.0)	
Job satisfaction			0.598
No	2 (14.3)	1 (6.7)	
Yes	12 (85.7	14 (93.3)	

IQR, interquartile range. Results for all parameters except age are given as n (%).

OFER-chronic fatigue subscale median (IQR) scores for Group A and Group B were 43.0 (33.00-58.50) and 63.0 (50.0-83.0), respectively (p=0.032). OFER-inter-shift fatigue subscale median (IQR) scores for Group A and Group B were 50.0 (37.00-57.75) and 37.0 (20.00-43.00), respectively (p=0.005). OFER-acute fatigue, ProQOL-compassion satisfaction, ProQOL-compassion fatigue, BDI scores were similar in both groups (**Table 2**).

Table 2. Comparison of Group A and Group B in terms of study scale scores

Parameter	Group A (n=14)	Group B (n=15)	p-value
OFER-chronic fatigue	43.0 (33.00-58.50)	63.0 (50.00-83.00)	0.032
OFER-acute fatigue	73.0 (61.50-77.75)	80.0 (63.00-83.00)	0.323
OFER-inter-shift fatigue	50.0 (37.00-57.75)	37.0 (20.00-43.00)	0.005
ProQOL-compassion satisfaction	36.5 (27.75-43.25)	30.0 (24.00-32.00)	0.110
ProQOL-compassion fatigue	16.0 (11.50-21.75)	20.0 (12.00-34.00)	0.382
BDI	10.0 (4.00-17.00)	15.0 (4.00-27.00)	0.405

OFER, occupational fatigue exhaustion/recovery scale; ProQOL, professional quality of life; BDI, Beck depression inventory

In binary logistic regression analysis, which included parameters with a statistically significant difference in univariate analysis between Group A and Group B, the odds ratios of OFER-chronic fatigue and OFER-inter-shift fatigue were 1.027 (95% CI 0.980-1.077, p=0.263) and 0.904 (95% CI 0.828-0.988, p=0.025), respectively (**Table 3**).

Table 3. Binary logistic regression analysis of parameters that could affect burnout levels

Parameter	OR	95% CI		p-value
		Lower	Upper	
OFER-chronic fatigue	1.027	0.980	1.077	0.263
OFER-inter-shift fatigue	0.904	0.828	0.988	0.025

OFER, occupational fatigue exhaustion/recovery scale; OR, odds ratio

DISCUSSION

In the current study we conducted with oncology nurses whose burnout level is expected to be high, we found that inter-shift fatigue (recovery) is the only independent predictive factor that affects burnout. To the best of our knowledge, there is no study in the literature investigating the relationship between inter-shift fatigue (recovery) and burnout in oncology nurses. Our study is valuable because it is the first study to draw attention to this issue.

Gluschkoff et al. (29) in a cross-sectional study of Finnish primary school teachers, showed that both job stress and inadequate recovery have contributed to the development of burnout. However, the role of recovery as an intermediary mechanism linking work stress to burnout has not been adequately addressed in this trial (29). In a cross-sectional survey with 573 cancer workers, where oncology nurses represent the most prominent professional group (n=211), the two recovery experiences of psychological detachment and relaxation had a strong negative association to burnout and psychological well-being (30). In another study examining the mediating effect of recovery experience on burnout and quality of life in female nurses in China, as a mediating factor, recovery experience has been shown to alleviate the impact of job burnout on quality of life (31). In a multicentre study by Fauzi et al. (32) where they included Malaysian public hospital doctors, acute and chronic fatigue were correlated, and both were negatively correlated with inter-shift recovery. Rumination on being scolded/violated was found to be negatively associated with recovery in this study (32). Work-related ruminations during the non-work time were typical and associated with poor fatigue and recovery outcomes (32). Nurses working in 12-hour shifts have experienced moderate to high levels of acute fatigue, moderate chronic fatigue and recovery between shifts, and an unhealthy fatigue recovery period (21). Consistent with previous studies, in another study, high levels of professional fatigue among nurses and poor recovery between shifts were associated with lack of care (33). Our findings and literature data suggest that the most determining factor for burnout in oncology nurses may be inter-shift fatigue (recovery).

There is insufficient literature data on evaluating the relationship between chronic fatigue and burnout in nurses. Rahman et al. (34) showed a statistically significant relationship between chronic fatigue and burnout in the simple linear regression model in their study with 201 emergency and intensive care nurses. However, the statistical significance of this relationship did not continue in the multiple linear regression model analysis (34). Similarly, in our study, although chronic fatigue is not an independent predictive factor for burnout, chronic fatigue was significantly higher in the group with high burnout than those with low burnout. Based on this finding, we think that chronic fatigue level may be a determining factor for burnout.

Previous research has found strong links between burnout and depression (35,36). In a study by Duan-Porter et al. (37) there was a positive relationship between mental disorder symptoms and burnout among nurses, and burnout was significantly associated with higher levels of anxiety, stress, and depression. Similarly, in a study designed to predict burnout levels among Canadian nurses (n=3257; 94.3% women), participants with clinically significant burnout were more likely to screen positive for all mental disorders, particularly major depressive disorder with a 43 fold risk, than participants

without burnout (38). A quantitative, descriptive, cross-sectional study involving 91 intensive care nurses, 10.98% of the nurses had depression symptoms and 14.29% burnout, showed that there is a positive correlation between the burnout dimension score and the BDI score (39). In our study, median BDI score was numerically higher in the group with a high burnout score than the group with a low burnout score. However, this difference was not statistically significant, possibly due to the low number of participants in the current study. Significant literature data support showing the relationship between depression and burnout made us think that the numerical difference in the BDI score in our study is remarkable.

The main limitation of our study is that it was conducted in a single center and with a limited number of participants. Studies with larger numbers of participants and multi-center studies can both increase the statistical power and reveal whether there is a difference between the centers in terms of burnout of oncology nurses.

CONCLUSION

Our study revealed that the most crucial factor related to the occupational burnout of nurses might be inter-shift fatigue (recovery). Chronic fatigue may also have an effect on occupational burnout. It should also be kept in mind that occupational burnout can lead to psychiatric illnesses such as depression. Understanding the relationship between burnout and inter-shift fatigue (recovery) may allow interventions to be made to prevent the work environment from being a trigger for burnout. Adding regulations on recovery to improvement programs regarding working conditions in nurses may prevent the path to burnout. New studies, such as comparative intervention studies (i.e., group therapies, occupational therapies) aimed at inter-shift fatigue (recovery), with a larger number of participants, are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted after the approval of the Ankara Onkoloji Training and Research Hosipital Clinical Researchs Ethics Committe (Date: 21.04.2021, Decision No: 2021-04/1128).

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 approved the final version.

REFERENCES

1. Kim K, Han Y, Kwak Y, Kim JS. Professional quality of life and clinical competencies among Korean nurses. Asian Nurs Res (Korean Soc Nurs Sci) 2015; 9: 200-6.
2. Zajac LM, Moran KJ, Groh CJ. Confronting compassion fatigue: assessment and intervention in inpatient oncology. Clin J Oncol Nurs 2017; 21: 446-53.
3. Stamm BH. The Concise ProQOL Manual. 2nd Edition ed: Pocatello, 2010.
4. Woo T, Ho R, Tang A, Tam W. Global prevalence of burnout symptoms among nurses: A systematic review and meta-analysis. J Psychiatr Res 2020; 123: 9-20.
5. Aycock N, Boyle D. Interventions to manage compassion fatigue in oncology nursing. Clin J Oncol Nurs 2009; 13: 183-91.
6. Jang I, Kim Y, Kim K. Professionalism and professional quality of life for oncology nurses. J Clin Nurs 2016; 25: 2835-45.
7. Zhang LF, You LM, Liu K, et al. The association of Chinese hospital work environment with nurse burnout, job satisfaction, and intention to leave. Nurs Outlook 2014; 62: 128-37.
8. White EM, Aiken LH, McHugh MD. Registered nurse burnout, job dissatisfaction, and missed care in nursing homes. J Am Geriatr Soc 2019; 67: 2065-71.
9. Russell K. Perceptions of burnout, its prevention, and its effect on patient care as described by oncology nurses in the hospital setting. Oncol Nurs Forum 2016; 43: 103-9.
10. Coetzee SK, Klopper HC. Compassion fatigue within nursing practice: a concept analysis. Nurs Health Sci 2010; 12: 235-43.
11. Neville K, Cole DA. The relationships among health promotion behaviors, compassion fatigue, burnout, and compassion satisfaction in nurses practicing in a community medical center. J Nurs Adm 2013; 43: 348-54.
12. Yoder EA. Compassion fatigue in nurses. Appl Nurs Res 2010; 23: 191-7.
13. Di Muzio M, Dionisi S, Di Simone E, et al. Can nurses' shift work jeopardize the patient safety? A systematic review. Eur Rev Med Pharmacol Sci 2019; 23: 4507-19.
14. Akman O, Ozturk C, Bektas M, Ayar D, Armstrong MA. Job satisfaction and burnout among paediatric nurses. J Nurs Manag 2016; 24: 923-33.
15. Rose DM, Seidler A, Nübling M, et al. Associations of fatigue to work-related stress, mental and physical health in an employed community sample. BMC Psychiatry 2017; 17: 167.
16. Fang JB, Zhou CF, Huang J, Qiu CJ. Psychometric properties of the chinese version of the occupational fatigue exhaustion/recovery scale: a test in a nursing population. J Nurs Res 2018; 26: 191-8.
17. Liu Y, Wu LM, Chou PL, Chen MH, Yang LC, Hsu HT. The influence of work-related fatigue, work conditions, and personal characteristics on intent to leave among new nurses. J Nurs Scholarsh 2016; 48: 66-73.
18. Wan JJ, Qin Z, Wang PY, Sun Y, Liu X. Muscle fatigue: general understanding and treatment. Exp Mol Med 2017; 49: e384.
19. Al Ma'mari Q, Sharour LA, Al Omari O. Fatigue, burnout, work environment, workload and perceived patient safety culture among critical care nurses. Br J Nurs 2020; 29: 28-34.
20. Winwood PC, Winefield AH, Dawson D, Lushington K. Development and validation of a scale to measure work-related fatigue and recovery: the Occupational Fatigue Exhaustion/Recovery Scale (OFER). J Occup Environ Med 2005; 47: 594-606.
21. Chen J, Davis KG, Daraiseh NM, Pan W, Davis LS. Fatigue and recovery in 12-hour dayshift hospital nurses. J Nurs Manag 2014; 22: 593-603.
22. Han K, Trinkoff AM, Geiger-Brown J. Factors associated with work-related fatigue and recovery in hospital nurses working 12-hour shifts. Workplace Health Saf 2014; 62: 409-14.

23. Caruso CC. Negative impacts of shiftwork and long work hours. Rehabil Nurs 2014; 39: 16-25.
24. Winwood PC, Winefield AH, Lushington K. Work-related fatigue and recovery: the contribution of age, domestic responsibilities and shiftwork. J Adv Nurs 2006; 56: 438-49.
25. Havlioglu S, Ortabag T, Winwood PC. Turkish validity and reliability of the occupational fatigue exhaustion/recovery scale. Medicine 2019; 8: 916-922.
26. Yeşil A, Ümit E, Cumhur A, Fatih ER, Olgun N, Aker A. Validity and reliability of the Turkish version of the professional quality of life scale. Nöropsikiyatri Arşivi 2010; 47.
27. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-71.
28. Hisli N. Beck depresyon envanterinin universite ogrencileri icin gecerliligi, guvenilirligi. (A reliability and validity study of Beck Depression Inventory in a university student sample). J Psychol 1989; 7: 3-13.
29. Gluschkoff K, Elovainio M, Kinnunen U, et al. Work stress, poor recovery and burnout in teachers. Occup Med (Lond) 2016; 66: 564-70.
30. Poulsen MG, Poulsen AA, Khan A, Poulsen EE, Khan SR. Recovery experience and burnout in cancer workers in Queensland. Eur J Oncol Nurs 2015; 19: 23-8.
31. Yang F, Ding J, Ma R, et al. Recovery experience: a concept for maintaining quality of life and its mediating effect among female nurses in China. Psychol Res Behav Manag 2020; 13: 831-41.
32. Mohd Fauzi MF, Mohd Yusoff H, Mat Saruan NA, Muhamad Robat R, Abdul Manaf MR, Ghazali M. Fatigue and recovery among Malaysian doctors: the role of work-related activities during non-work time. BMJ Open 2020; 10: e036849.
33. Min A, Kim YM, Yoon YS, Hong HC, Kang M, Scott LD. Effects of work environments and occupational fatigue on care left undone in rotating shift nurses. J Nurs Scholarsh 2021; 53: 126-36.
34. Rahman HA, Abdul-Mumin K, Naing L. A study into psychosocial factors as predictors of work-related fatigue. Br J Nurs 2016; 25: 757-63.
35. Koutsimani P, Montgomery A, Georganta K. The relationship between burnout, depression, and anxiety: a systematic review and meta-analysis. Front Psychol 2019; 10: 284.
36. Carmassi C, Bertelloni CA, Avella MT, et al. PTSD and burnout are related to lifetime mood spectrum in emergency healthcare operator. Clin Pract Epidemiol Ment Health 2020; 16: 165-73.
37. Duan-Porter W, Hatch D, Pendergast JF, et al. 12-month trajectories of depressive symptoms among nurses-Contribution of personality, job characteristics, coping, and burnout. J Affect Disord 2018; 234: 67-73.
38. Stelnicki AM, Jamshidi L, Angehrn A, Hadjistavropoulos HD, Carleton RN. Associations between burnout and mental disorder symptoms among nurses in Canada. Can J Nurs Res 2020: 844562120974194.
39. Vasconcelos EM, Martino MMF, França SPS. Burnout and depressive symptoms in intensive care nurses: relationship analysis. Rev Bras Enferm 2018; 71: 135-41.

Original Article

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Evaluation of mortality and acute kidney injury by KDIGO and RIFLE in patients treated with colistin in the intensive care unit

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ABSTRACT

Introduction: Multidrug-resistant bacterial infections such as *pseudomonas aeruginosa*, *Acinetobacter baumannii*, *klebsiella pneumoniae* are common in Intensive Care Units. Colistin is preferred today due to limited treatment options sensitive to these pathogens. However, colistin has a high potential for nephrotoxicity. Some classifications (KDIGO, RIFLE, AKIN) are used for the diagnosis of Acute Kidney Injury (AKI). The incidence of AKI varies according to these classifications. In our study, we aimed to evaluate and compare the development of Acute Kidney Injury according to KDIGO criteria and RIFLE classification in patients followed up in the intensive care unit and started colistin therapy.

Materials and Method: The data of 145 patients who started colistin treatment in the Internal Medicine Intensive Care Unit between January 2016 and December 2019 were retrospectively reviewed. Patients were grouped as those with Acute Kidney Injury and those without. Acute Kidney Injury evaluation was made according to RIFLE classification and KDIGO criteria.

Results: In patients who received colistin treatment, 75 patients were evaluated as AKI when KDIGO criteria were used for the AKI diagnosis, and 54 patients were evaluated as AKI when the RIFLE classification was used. While the number of KDIGO Stage 1 patients was 44, the number of patients in the RIFLE classification risk group was determined as 23. The mean SOFA score was calculated as 7.91±2.8 and the mean APACHE II score as 22.77±5.3. The duration of stay in the ICU was 22.60±9.04. The duration of stay in the ICU was shorter in the group who developed AKI. 44.8% of the patients included in the study died. 52% of patients who developed AKI and 37.1% of those who did not develop AKI died. 30-day mortality in patients with AKI was significantly higher than both KDIGO staging and RIFLE classification (p=0.03, p=0.005, respectively). Mortality rate increased 1.42 times in KDIGO Stage 1, 2.79 times in KDIGO Stage 2 and 2.10 times in KDIGO Stage 3. When evaluated by the RIFLE classification, the mortality rate increased 2.32 times in the Risk group, 3.12 times in the Injury group, 2.06 times in the Failure group and 2.15 times in the Loss group.

Conclusion: We observed an increase in the frequency of AKI in patients using colistin in the ICU, both according to KDIGO criteria and the RIFLE classification. This situation also increases the 30-day mortality. We think that the KDIGO criteria are more sensitive to diagnose AKI in these patients.

Keywords: Colistin, acute kidney injury, intensive care units

INTRODUCTION

In recent years, an increase in multi-drug resistant (MDR) bacterial infections has been observed in patients followed in Intensive Care Units (ICU). These infections prolong hospital stay and increase mortality and morbidity (1). Colistin is preferred among polymyxin group polypeptide antibiotics, due to the limited treatment options available that are sensitive to these multidrug-resistant pathogens such as *Acinetobacter baumannii*, *pseudomonas aeruginosa*, *klebsiella pneumoniae* (2). Polymyxins are divided into 5 groups (A-E) and some of them (A, C, D) are not used today due to their severe toxicity. Only polymyxin B and polymyxin E (also known as colistin) are in clinical use (3). The most important side effect of colistin is nephrotoxicity. As a result of the studies conducted, the rate of developing acute kidney injury (AKI) after colistin treatment ranges between 20-60% (4). Colistin causes cell swelling and cell lysis by increasing the permeability of the tubular epithelial

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cell membrane. Nephrotoxicity is dose dependent and reversible, although not always (5). Early recognition of nephrotoxicity can be achieved with closer follow-up in patients who were given colistin. RIFLE (Risk, Injury, Failure, Loss, End stage kidney disease) classification for AKI definition and Kidney Disease Improving Global Outcomes (KDIGO) criteria are used. In our study, we aimed to determine the development of AKI in patients receiving colistin treatment in intensive care units as per the RIFLE classification and KDIGO criteria, and its correlation with the risk factors related to nephrotoxicity, frequency of nephrotoxicity and mortality.

MATERIAL AND METHOD

Approval for the study was granted by the Ethics Committee of Dicle University Medical Faculty (Date: 05.03.2020, Decision No: 254). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of 145 patients who received colistin treatment in the General Internal Medicine Intensive Care Unit between 2016 and 2019 were retrospectively analyzed. Patients >18 years of age who received colistin treatment for longer than 48 hours, regardless of gender, were included in the study. Patients with pre-treatment acute kidney injury and chronic kidney damage who received colistin for less than 48 hours were excluded from the study. Colistin was administered to the patients at a dose of 300 mg/day. Demographic characteristics (age and gender) of the patients were evaluated. Acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) score were calculated at the time of admission. The method of use of colistin (IV, IV+inhaler, inhaler), pre-treatment basal laboratory values, focus of infection, isolated microorganisms, duration of intensive care stay, and results were recorded. Serum creatinine levels of the patients were analyzed from the day of colistin initiation. Acute kidney injury staging was performed using RIFLE classification and KDIGO criteria to evaluate renal damage. The patients were divided into two groups, according to the RIFLE classification and KDIGO criteria, with or without acute kidney injury.

Statistical Evaluation

Statistical analysis of the results obtained in the study was performed using the SPSS (Statistical Package for Social Sciences) 24 program. Descriptive statistics were used for demographic data. The normal distribution suitability of the variables were examined using visual (histogram and probability plots) and analytical methods (Kolmogrov-Simirnov/Shapiro-Wilk tests). Results are given as numbers and percentages for categorical variables and as mean±standard deviations for continuous variables. Independent sample t-test was applied as parametric test to those with normal distribution, and Mann-Whitney U test as non-parametric test was applied to those who did not show normal distribution. Comparison of the data of the groups with and without AKI was made using Chi-square and Fisher's tests. Kaplan-Meier method was used for survival analysis and compared using log rank analysis. Cox Regression analysis was used for the analysis of variables related to mortality. A p value of less than 0.05 was considered statistically significant.

RESULTS

The data of 145 patients who were given colistin were analyzed. 86 (59.3%) of these patients were female and 59 (40.7%) were male. The mean age of the patients was 64.9±16.8 years. Pneumonia was in the first place with 51% as the focus of infection. The most common microorganisms isolated in blood culture were *A. baumanii*, *K. pneumonia* and *P. Aeruginosa* (50.3%, 16.6%, 10.3%, respectively). Colistin treatment was given as intravenous (IV) to 125 patients, IV and inhaler to 13 patients, and only inhaler to 7 patients.

75 patients were evaluated as AKI when KDIGO criteria were used for the AKI diagnosis, and 54 patients were evaluated as AKI when the RIFLE classification was used. 44 patients were classified as Stage 1, 15 patients as Stage 2, 16 patients as Stage 3 according to KDIGO staging, and 23 patients were classified as Risk, 16 as Injury, 13 as Failure, and 2 as Loss according to RIFLE classification. While the mean age in the group with AKI was calculated as 66.9±15.5, the mean age in the group without AKI was calculated as 62.4±17.9. Although AKI was more common in elderly patients, no statistical difference was found (p=0.183). No difference was found between the groups in terms of gender (p: 0.608). AKI did not develop in patients who were given inhaled colistin. No statistically significant difference was found in the development of AKI in those who were given IV or IV+inhaler treatment (p>0.05). Besides, RRT was applied to 29 of the patients who developed AKI.

The APACHE II scores and SOFA score of the patients were calculated at the time of diagnosis. The mean SOFA score was calculated as 7.91±2.8 and the mean APACHE II score as 22.8±5.3. In patients who developed AKI, the SOFA score was found as 8.8±2.9, and the APACHE II score as 24±5.4. In patients who did not develop AKI, the SOFA score was calculated as 6.8±2.2, and the APACHE II score as 21.3±4.7. SOFA and APACHE II scores were found to be significantly higher in patients with AKI (p: 0.03, p: 0.027, respectively). Comparison of the groups by the demographic, clinical and laboratory characteristics is shown in **Table 1**.

Tablo 1. Demographic, clinical and laboratory characteristics of the groups				
	All Patients (n:145) Mean±SD	**Non-AKI (n:70) Mean±SD**	**AKI (n:75) Mean±SD**	**p**
Female Male	86 (59.3%) 59 (40.7%)	40 (57.1%) 30 (42.9%)	46 (61.3%) 29 (38.7%)	0.608
Age	64.88±16.77	62.39±17.87	66.86±15.50	0.183
Urea (mg/dL)	95.43±64.71	46.24±25.88	119.77±64.38	<0.001
Creatinine (mg/dL)	1.92±1.68	0.62±0.26	2.56±1.72	<0.001
Albumin (g/dL)	2.19±0.42	2.27±0.49	2.14±0.38	0.117
Uric acid (mg/dL)	5.12±2.84	3.23±1.61	6.06±2.86	0.002
SOFA score	7.9±2.8	6.8±2.2	8.8±2.9	0.03
APACHE II	22.8±5.3	21.3±4.7	24±5.4	0.027
Microorganisms *A. baumanii* *K. pneumonia* *P. Aeruginosa* Another microorganism No reproduction	 73 (50.3%) 24 (16.6%) 15 (10.3%) 17 (11.7%) 16 (11%)	 38 (54.3%) 12 (17.1%) 9 (12.9%) 6 (8.6%) 5 (7.1%)	 35 (46.7%) 12 (16%) 6 (8%) 11 (14.7%) 11 (14.7%)	
Survivor Ex	80 (55.2%) 65 (44.8%)	44 (62.9%) 26 (37.1%)	36 (48%) 39 (52%)	0.072
ICU length of stay (days)	22.60±9.04	24.2±8.47	21.12±9.36	0.04
WBC: White Blood Cell, RDW: Red Cell Distribution Width, SOFA: Sequential Organ Failure Assessment, ICU: Intensive care unit				

65 (44.8%) of the patients included in the study died. 52% (n:39) of patients who developed AKI and 37.1% (n: 26) of those who did not develop AKI died (p=0.02). Mortality numbers according to AKI classification methods and stages are shown in **Table 2**.

Table 2. AKI staging and mortality			
	All patients (n:145)	**Ex (n:65)**	**Survivor (n:80)**
RIFLE			
Non-AKI	91 (62.8%)	33 (50.8%)	58 (72.5%)
R	23 (15.9%)	14 (21.5%)	9 (11.3%)
I	16 (11%)	8 (12.3%)	8 (10%)
F	13 (9%)	9 (13.8%)	4 (5%)
L	2 (1.4%)	1 (1.5%)	1 (1.3%)
KDIGO			
Non-AKI	70 (48.3%)	26 (40%)	44 (55%)
Stage 1	44 (30.3%)	21 (32.3%)	23 (28.8%)
Stage 2	15 (10.3%)	7 (10.8%)	8 (10%)
Stage 3	16 (11%)	11 (16.9%)	5 (6.3%)

The mean duration of stay in the ICU was 22.60±9.04. The duration of stay in the ICU was found to be significantly lower in the group who developed AKI (p:0.04). As per the Kaplan-Meier analysis, 30-day mortality in patients with AKI was significantly higher than both KDIGO staging and RIFLE classification (p=0.03, p=0.005, respectively) (**Figure 1-2**)

When assessed by COX regression analysis, the risk of death was 1.42-fold higher in KDIGO Stage 1 patients, 2.79-fold higher in KDIGO Stage 2 patients, and 2.10-fold higher in KDIGO Stage 3 patients compared to non-AKI patients. When evaluated by the RIFLE classification, the risk of death was 2.32 times higher in the risk group, 3.12 times higher in the Injury group, 2.06 times higher in the Failure group and 2.15 times higher in the Loss group compared to the non-AKI group. (**Table 3**)

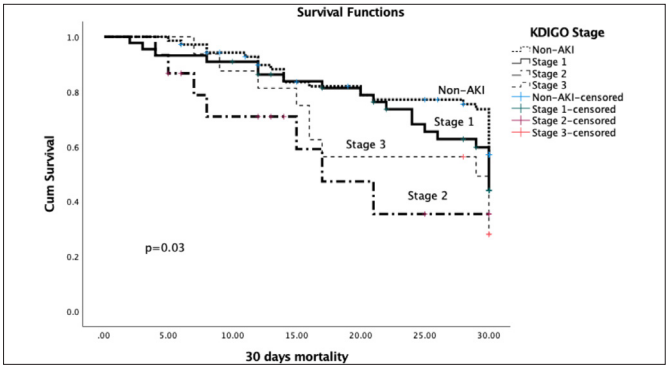

Figure 1. Kaplan-Meier survival analysis for KDIGO Stage

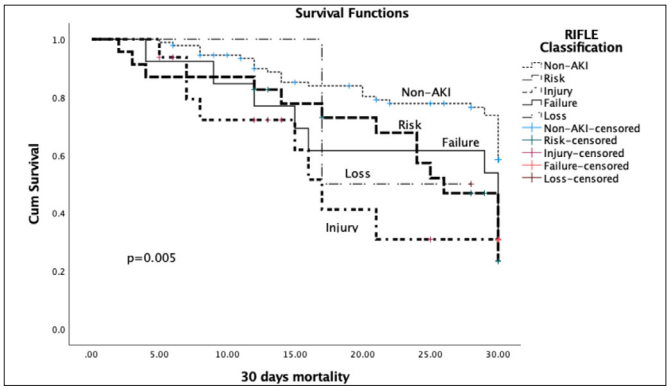

Figure 2. Kaplan-Meier survival analysis for RIFLE Classification

Table 3. Cox regression analysis for 30 days mortality			
Variables	**OR**	**95% CI**	**p**
KDIGO			
Stage 1	1.42	0.80-2.53	0.226
Stage 2	2.79	1.19-6.49	0.017
Stage 3	2.10	1.03-4.25	0.039
RIFLE			
Risk	2.32	1.23-4.36	0.009
Injury	3.12	1.42-6.84	0.004
Failure	2.06	0.98-4.32	0.053
Loss	2.15	0.29-15-89	0.453
OR: odds ratio, CI: Confidence Interval			

DISCUSSION

In the present day, colistin has begun to be reused in the treatment of multidrug-resistant gram-negative bacteria due to the limited treatment options available. The most important disadvantage of this drug is that it is nephrotoxic. Nephrotoxicity rates developing due to colistin use vary between 20-60% (4). This variability in nephrotoxicity rates is thought to arise from different patient populations and the use of various criteria (RIFLE, AKIN, KDIGO) (6).

After the use of colistin, there are studies that have detected AKI using the RIFLE classification. Hartzell et al. (7) reported the incidence of AKI as 45% in their study including 66 patients. Kwon JA et al. (8) found the incidence of AKI in 71 critical patients as 54%, and Kaya M et al. (9) found 69.7% in patients in the ICU of the oncology hospital. Considering the studies diagnosed with AKI using KDIGO criteria, Günay et al. (4) reported the incidence of AKI as 64.4% in their study in which they analyzed the data of 149 patients. Giacobbe et al. (10) found the incidence of AKI as 68.8% in their study including 170 patients, and Yu et al. (11) found 46.7% in their multi-center study in which 295 patients were included. In our study, we evaluated the development of AKI in patients who were given colistin treatment as per both RIFLE classification and KDIGO criteria. In the study, we found the rate of AKI development as 37.2% (n:54) when the RIFLE classification was used, and 51.7% (n:75) when the KDIGO criteria were used. The reason for this difference is that while 1.5-fold increase in serum creatinine level in RIFLE classification is classified as risk group, serum creatinine level 0.3 mg/dL or baseline creatinine 1.5-2-fold increase is accepted as Stage 1 as per the KDIGO criteria. Considering this situation, patients who do not meet the RIFLE classification risk group criteria can be classified as KDIGO Stage 1 AKI. Therefore, the classification preferred for the diagnosis of AKI affects the incidence of AKI. In our study, the number of patients who developed AKI stage 1 was 44 while the number of patients in the RIFLE Risk stage was 23. As a result of our study, we found that KDIGO criteria may be more sensitive in diagnosing AKI.

The risk of developing AKI increases in elderly patients. When the literature is reviewed, AKI after colistin is observed more frequently in elderly patients (4,12,13). In our study, the average age of the patients who developed AKI was higher.

APACHE II and SOFA scores calculated in critically ill patients hospitalized in ICU are used to predict prognosis. Kidney function tests are also evaluated in both scoring systems. The risk of AKI increases in patients with high APACHE II and SOFA scores (14). In our study, AKI was found to be statistically significantly higher in patients with high APACHE II and SOFA scores calculated at the time of admission to the hospital (p=0.027, p=0.03, respectively).

The development of AKI and the advanced stage of AKI increase mortality in patients followed in the ICU (15-17). In our study, we investigated the relationship between AKI and mortality. 52% of patients who developed AKI and 37.1% of those who did not develop AKI died (p=0.02). We compared the mortality rates of our patients with AKI according to KDIGO criteria and RIFLE classification. Mortality was found to be statistically significantly higher in KDIGO Stage 2 and 3 mortality was significantly higher in Risk and Injury group according to RIFLE classification.

Our study has some limitations. The fact that the study has a retrospective design can be considered as the main limitation. Besides, the limited number of our patients due to the fact that the study was single-centered and was not a combined ICU is an important limitation. Multicenter prospective studies involving different patient populations may provide stronger results.

CONCLUSION

As a result, the use of colistin has become mandatory due to the limited alternative antibiotic treatment options other than colistin in MDR Gram-negative bacterial infections. Our data showed that the incidence of AKI was increased in critically ill patients using colistin. Tthe classification preferred for the diagnosis of AKI affects the incidence of AKI. We think that the KDIGO criteria are more sensitive to diagnose AKI in these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of Dicle University Medical Faculty (Date: 05.03.2020, Decision No: 254).

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.

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. Cerceo E, Deitelzweig SB, Sherman BM, et al. Multidrug-resistant Gram-negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerging treatment options. Microb Drug Resist 2016; 22: 412–31.
2. Kınıklı S, Cesur S, Yücel M, Hatipoğlu ÇA, Dinç B. Determination of polymyxin B, minocycline, colistin and phosphomycin susceptibilities in *Acinetobacter baumannii* strains showing carbapenem resistant multidrug resistance phenotype. J Health Sci Med 2019; 2: 49-53.
3. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005; 40: 1333-41.
4. Gunay E, Kaya S, Baysal B, Yuksel E, Arac E. Evaluation of prognosis and nephrotoxicity in patients treated with colistin in intensive care unit. Ren Fail 2020; 42: 704-9.
5. Javan AO, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. Eur j Clin Pharmacol 2015; 71: 801-10.
6. Incı A, Toker MK, Bicer IG, Derbent A, Salihoglu Z. Determination of colistin-related nephrotoxicity and risk factors in intensive care unit. North Clin Istanb 2018; 5: 120-4.
7. Hartzell JD, Neff R, Ake J, et al. Nephrotoxicity associated with intravenous colistin (Colistimethate sodium) Treatment at a Tertiary Care Medical Center. Clinical Infectious Diseases 2009; 48: 1724-8.
8. Kwon JA, Lee JE, Huh W, et al. Predictors of acute kidney injury associated with intravenous colistin treatment. Int J Antimicrob Agents 2010; 35: 473-7.
9. Kaya M, Tunçel Yİ, Kuru RN, et al. Onkoloji hastanesi yoğun bakım ünitesinde kolistin ilişkili nefrotoksisitenin retrospektif değerlendirilmesi. Türk Yoğun Bakım Derneği Derg 2014; 12: 51-6.
10. Giacobbe DR, Masi AD, Leboffe L, et al. Hypoalbuminemia as a predictor of acute kidney injury during Colistin treatment. Sci Rep 2018 10; 8: 11968.
11. Yu SN, Kim T, Park SY, et al. Predictors of acute kidney injury and 28-day mortality in carbapenem-resistant *Acinetobacter baumannii* complex bacteremia. Microb Drug Resist 2021; 10.1089/mdr.2020.0312.
12. Ciftci A, Izdes S, Altintaş ND. Factors determining nephrotoxicity and mortality in critical care patients receiving colistin. J Infect Dev Ctries 2018; 11: 912-8.
13. Deryke CA, Crawford AJ, Uddin N, Wallace MR. Colistin dosing and nephrotoxicity in a large community teaching hospital. Antimicrob Agents Chemother 2010; 54: 4503-5.
14. Søvik S, Isachsen MS, Nordhuus KM, et al. Acute kidney injury in trauma patients admitted to the ICU: a systematic review and meta-analysis. Intensive Care Med 2019; 45: 407-19.
15. Aydın E, Kadiroglu AK, Yılmaz Aydın F, et al. The relationship between acute kidney injury and inflammation-based parameters and mortality in oncologic intensive care patients. J Crit Intensive Care 2020; 11: 50–4.
16. Vieira JM Jr, Castro I, Curvello-Neto A, et al. Effect of acute kidney injury on weaning from mechanical ventilation in critically ill patients. Crit Care Med 2007; 35: 184–91.
17. Hoste EAJ, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41: 1411-23.

Original Article

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Assessment of Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios, in patients with COVID-19 infected with or without pneumonia

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ABSTRACT

Objective: COVID-19 infection has the potential to affect the cardiovascular system as well as respiratory disease. Recent studies have suggested that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios may be associated with ventricular arrhythmias. The goal of this study is to the evaluation of Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios, in patients with COVID-19 infected with or without pneumonia.

Material and Method: 118 patients with COVID-19 infection were divided into 2 groups: patients with and without pneumonia, the control group consisted of 39 people. The Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio were gauged by the 12-lead electrocardiogram.

Results: Tp-e interval, Tp-e/QT, Tp-e/QTc ratio were considerably high in COVID-19 patients with pneumonia, contrasted to the without pneumonia patients. ($p < 0.01$, $p < 0.01$, $p < 0,01$, respectively) whereas the same parameters were similar to the control group in COVID-19 infected patients without pneumonia. ($p=0.258$, $p=0.249$, $p=0,056$, respectively). Correlation analysis revealed a significant and positive correlation between CRP with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. There was the same correlation relationship between WBC with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

Conclusion: Our present study showed that Tp-e interval, Tp-e/QT, Tp-e/QTc ratio were prolonged in COVID-19 infected patients with pneumonia.

Keywords: COVID-19, Tp-e interval, Tp-e/QT and Tp-e/QTc

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which originated in China in late December 2019 and was effective all over the world in a very short time, was declared as a pandemic by the World Health Organization.

COVID-19 named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel RNA virus that induces acute pneumonia that can lead to severe respiratory distress syndrome, which may be fatal. Nonetheless, many infections are mild or asymptomatic (1,2).

Although COVID-19 primarily affects the lungs, it can also affect multiple organs, especially the cardiovascular system. Acute cardiovascular events complicating the clinical course of COVID-19 may be one of the causes of poor survival. One of the most common cardiac complications during this disease is arrhythmias (3,4). It has been shown that the arrhythmic event was observed between 7% to 44% depending on the severity of the disease (5). Arrhythmias such as atrial fibrillation, conduction blocks, ventricular tachycardia, and ventricular fibrillation have been shown to occur in the course of COVID-19 (3,4).

In ECG, research of ventricular recovery and augmented dispersion of repolarization are useful markers for ventricular arrhythmias. Some ventricular repolarization markers are useful to predict arrhythmias, including the QT interval, QT dispersion, and T-wave alternans (6,7).

Recent studies have suggested that new indexes such as Tpeak-Tend (Tp-e) interval, and Tp-e interval/QT interval (Tp-e/QT) ratio may be associated with ventricular arrhythmias in various clinical scenarios (8,9).

We purposed to examine the changes in Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in adults infected COVID-19 patients with and without pneumonia.

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MATERIAL AND METHOD

Ethical approval for the study was granted by Kayseri City Hospital Clinical Research Ethics Committee (Date: 25.06.2020, Decision No: 135). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study population

Our study was designed as a single-center study regarding the confirmed COVID-19 patients monitored and treated in inpatient clinics, or the intensive care units (ICUs).

The study was carried out in our hospital, which accepted COVID-19 patients who were confirmed by molecular methods determined by the Ministry of Health of Turkey as ' COVID-19 Hospitals'. Electrocardiographic data of the patients were recorded, including the risk factors, as well as clinical, radiological, and laboratory findings.

Patients older than 18 years of age and were diagnosed as definite SARS-CoV2 in presence of symptoms and positive polymerase chain reaction (PCR) were analyzed. In this cross-sectional study, a total of 118 patients hospitalized with COVID-19 diagnosis between March and June 2020 in our hospital were evaluated. 39 well- sex and age-matched patients with randomized selected for the comparison were included in the study.

Patients were separated into two groups according to the clinical presentation based on the definitions in the "COVID-19 Diagnosis and Treatment Guide" printed by the Turkish Ministry of Health (10).

Group 1 Mild illness presents with features such as fever, muscle/joint pain, cough, sore throat, and nasal congestion, without pneumonia together with a respiratory rate <30/min and an O2 saturation above 90% while breathing room air.

Group 2 Severe illness is defined with widespread findings of pneumonia in chest radiography or computed tomography.

The first electrocardiogram (ECG) recording of patients at the time of hospital admission were analyzed. At that time, no patient was receiving any medical treatment. Patients with a history of ischemic heart disease, those with a history of heart valve disease, those with heart failure (left ventricular ejection fraction ≤50), those with a branch block or atrioventricular conduction disorder in the surface ECG, those with poor electrolyte imbalance, patients with poor ECG quality were excluded from the study.

The standard COVID-19 treatment protocol recommended by the Science Advisory Board of the Turkish Ministry of Health, including, hydroxychloroquine 200 mg twice daily, and azithromycin 250 mg once daily following a 500 mg loading dose were administered to all patients. In addition to patients with pneumonia, Oseltamivir phosphate 75mg was added twice Daily (10). Demographic data, findings of the imaging studies, and laboratory test results were retrieved from the institutional digital database.

If the serum levels of troponin I, one of the cardiac biomarkers, were below the upper reference limit of the 99th percentile or if there were no new abnormalities in electrocardiography and echocardiography, it was considered that there was no myocardial damage (11). Hypertension, Diabetes mellitus, and Hyperlipidemia defined as previously described (12). Smokers were current smokers and had been using for at least 10 years.

Electrocardiogram (ECG) Analysis

All standard 12-lead ECGs were acquired at rest in the supine position simultaneously using a recorder (Philips brand machine) set at 25 mm/s paper speed and 1 mV/cm standardization. All ECGs were scanned and transferred to personal computers an electronic caliper (Cardio Calipers, version 3.3 software; Iconico.com, Philadelphia, PA, USA) was used under magnification to record the measurements. Assessments of the ECG were done by 2 cardiologists blinded to the clinical data, and to diminish the error measurements. Patients whose ECGs showed U waves and negative T waves were excluded from the study.

The Tp-e interval was defined as the distance between the peak of the T-wave and the end of the T-wave. All Tp-e intervals were measured using the best available T-wave in lead V5 (13). When the lead V5 result was not suitable for analysis, the V4 and V6 were used.

The QT interval was measured from the beginning of the QRS complex to the end of the T wave in precordial lead V6, which best reflects the transmural axis of the left ventricle (14) and corrected for HR using the Bazett formula: cQT=QT$\surd$ (R–R interval. The Tp–e/QT ratio and Tp-e/QTc (Tp-e divided by QT and Tp-e divided by QTc) were calculated from these measurements. Interobserver and intraobserver coefficients of variation were less than 5%, respectively.

Echocardiography

Conventional echocardiography was performed with Philips Epiq 7 ultrasound system (Philips, Andover, Mass., USA). To reduce the risk of COVID-19 transmission, only LVEF and left ventricular dimensions were examined to detect myocardial damage. Conventional echocardiographic images were obtained from the parasternal and apical views The teichholz method was used for the calculation of LV

ejection fraction.

Statistical Analysis

Statistical analyzes were performed using SPSS Statistics Package version 21.0 (SPSS Inc, Chicago, IL, USA) for Windows. The normal distribution of variables was analyzed using the Kolmogorov-Smirnov method. Continuous data mean and standard deviations were evaluated and recorded. Continuous variable distribution among the groups was done by One Way Anova. Variability between groups was performed by the LSD test. The chi-square test was used for categorical variables and was calculated as a percentage. The relationship between the variables was analyzed by Pearson correlation analysis. P-value less than 0.05 was considered significant.

RESULTS

A total of 157 participants were selected in the current study. The COVID-19 group consisted of 118 subjects (64 men, 54 female), and the control group included 39 individuals (22 men,17 female). COVID-19 Patients were divided into two groups according to the presence of pneumonia. While 48 of these patients had no pneumonia (group 1), 70 had pneumonia (group 2).

Baseline clinical and demographic features of the study groups are presented in **Table 1**. The study population was similar regarding sex distribution, age, smoking status, frequencies of hypertension, and diabetes were not significantly different between patients and the control group (p> 0.05).

The baseline laboratory measurements of the study patients are listed in **Table 2**. Serum glucose, C-reactive protein (CRP), white blood cell (WBC), and platelet levels were significantly higher COVID -19 with pneumonia patients. (p<0,01, p<0,01, p<0,01, p<0,01 respectively). Other blood parameters were similar between groups. Troponin values in COVID patients with and without pneumonia were within the normal range. There was no difference between the groups.

The electrocardiographic and echocardiography parameters of the groups are shown in **Table 3**. LVEF, an indicator of LV systolic function, was similar between groups (p=0.432). The QRS duration, QT interval, and QTc interval were similar between the groups (p =0,054, p=0.858, p=0,221 respectively) Although heart rate in

Table 1. Baseline clinical and demographic features of the study groups

Variables	Control group (n=39)	Covid+ without pneumonia (n=48)	Covid+ with pneumonia (n=70)	p value
Age (years)	49±10.716	49.81±12.489	52.91±16.182	0.186
Male/female	22/17	25/23	39/31	0.901
HT	5	6	18	0.111
DM	2	2	9	0.173
Smoking	7	9	13	0.995

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. DM: Diabetes Mellitus, HT: Hypertension

Table 2. Comparison of baseline laboratory measurements among the study groups

Variables	Control group (39)	Covid+ without pneumonia (48)	Covid+ with pneumonia (70)	P value
Glucose (mg/dL)	86.41±8.303	98.42±26.026	107.23±25.043	<0.01*
Kreatinin (mg/dL)	0.849±0.176	0.804±0.186	0.888±0.288	0.162
AST (U/L)	22.36±6.247	20.65±7.292	23.86±12.308	0.211
ALT (U/L)	19.26±7.312	20.65±12.80	22.47±14.778	0.429
Total Bilirubin (mg/dL)	0.58±0.207	0.52±0.350	0.57±0.319	0.607
CRP	2.78±1.077	9.708±11.33	80.934±12.703	<0.01*
WBC (10^3/uL)	8.428±2.503	7.506±2.420	17.276±4.420	<0.01*
Hemoglobin (g/l)	13.682±1.738	13.913±1.9513	14.013±2.3727	0.115
Platelet (/mm3)	233.74±81.398	236.69±55.237	278.51±83.285	0.002*
Troponin I		<0.1	<0.1	1.000

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. WBC: white blood cell, P values that are lower than 0.05 are marked with *

Table 3. Electrocardiographic characteristics of the study population

Variables	Control group (39)	Covid+ without pneumonia (48)	Covid+ with pneumonia (70)	p
Heart rate (beat/min)	75.90±8.641	74.71±11.187	70.21±9.824	0.007*
QRS duration (ms)	84.72±8.392	98.96±28.896	84.89±10.001	0.054
QT interval (ms)	380.46±20.963	378.42±27.546	381.12±27.782	0.858
QTc interval (ms)	422.77±16.539	417.44±14.599	416.56±14.478	0.221
Tp-e (ms)	74.08±4.922	75.13±5.511	84.97±4.380	<0.01*
TPe/QTc ratio (ms)	0.175±0.011	0.179±0.11	0.209±0.010	<0.01*
TPe/QT ratio (ms)	0.195±0.015	0.199±0.019	0.223±0.017	<0.01*
LVEF (%)	65.05±4.57	64.25±4.31	63.97±3.88	0.432

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. Tp-e= T wave interval from peak to end, c=corrected, P values that are lower than 0.05 are marked with *

the ECG was within the normal range, COVID-19 with pneumonia was significantly lower.

Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly higher in COVID-infected with pneumonia patients compared to the COVID infected without pneumonia. (p<0.01) (**Figure 1**). Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were similar between COVID infected without pneumonia and control groups. (p=0,321, p=0,56, p=0,249) (**Figure 1**)

In correlation analysis revealed a significant and positive correlation between CRP with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio (r=0471, p =0,001; r=0,416, p=0,001; r=0,481, p=0,001 respectively) (**Figure 2**).

There was the same correlation relationship between WBC with Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. (r=550, p=0,001; r=0,478, p=0,001; r=0,602, p=0,001 respectively).

Thirty-two of the 70 patients with COVID pneumonia required intensive care, although cardiac death was observed in 3 patients, but documented ventricular arrhythmia was not detected in these patients. However, both of these patients had prolonged T-pe (96 msn,93 msn,91 msn respectively), and T-pe/QTc ratios (0.22, 0.21,0.21 respectively).

DISCUSSION

The most important result of our work is that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were prolonged in COVID-19 patients with pneumonia as compared to COVID-19 patients with mild disease without pneumonia. However, the results of COVID-19 patients with mild disease without pneumonia were similar to healthy ones. These findings may have an important role in the diagnosis and management of COVID-19 -related arrhythmias.

Table 4. Post hoc analysis

	Control group	Group 1	p	Control group	Group 2	p	Group 1	Group 2	p
Heart rate (beat/min)	75.90	74.71	0.582	75.90	70.21	.005*	74.71	70.21	0.018
QT (msn)	380.46	378.42	0.718	380.46	381.12	.903	378.42	381.12	0.585
QTc (msn)	422.77	417.44	0.102	422.77	416.56	.184	417.44	416.56	0.151
Tpe (msn)	74.08	75.13	0.258	74.08	84.97	<0.01	75.13	84.97	<0.01
TPe/QTc ratio (ms)	0.175	0.179	0.056	0.175	0.209	<0.01	0.179	0.209	<0.01
TPe/QT ratio (ms)	0.195	0.199	0.249	0.195	0.223	<0.01	0.199	0.223	<0.01
WBC	8.42	7.50	0.229	8.42	17.27	<0.01	7.50	17.27	<0.01
CRP	2.78	9.70	<0.01	2.78	80.93	<0.01	9.70	80.93	<0.01

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. Group1. Covid+without pneumonia, Group 2. Covid+with pneumonia

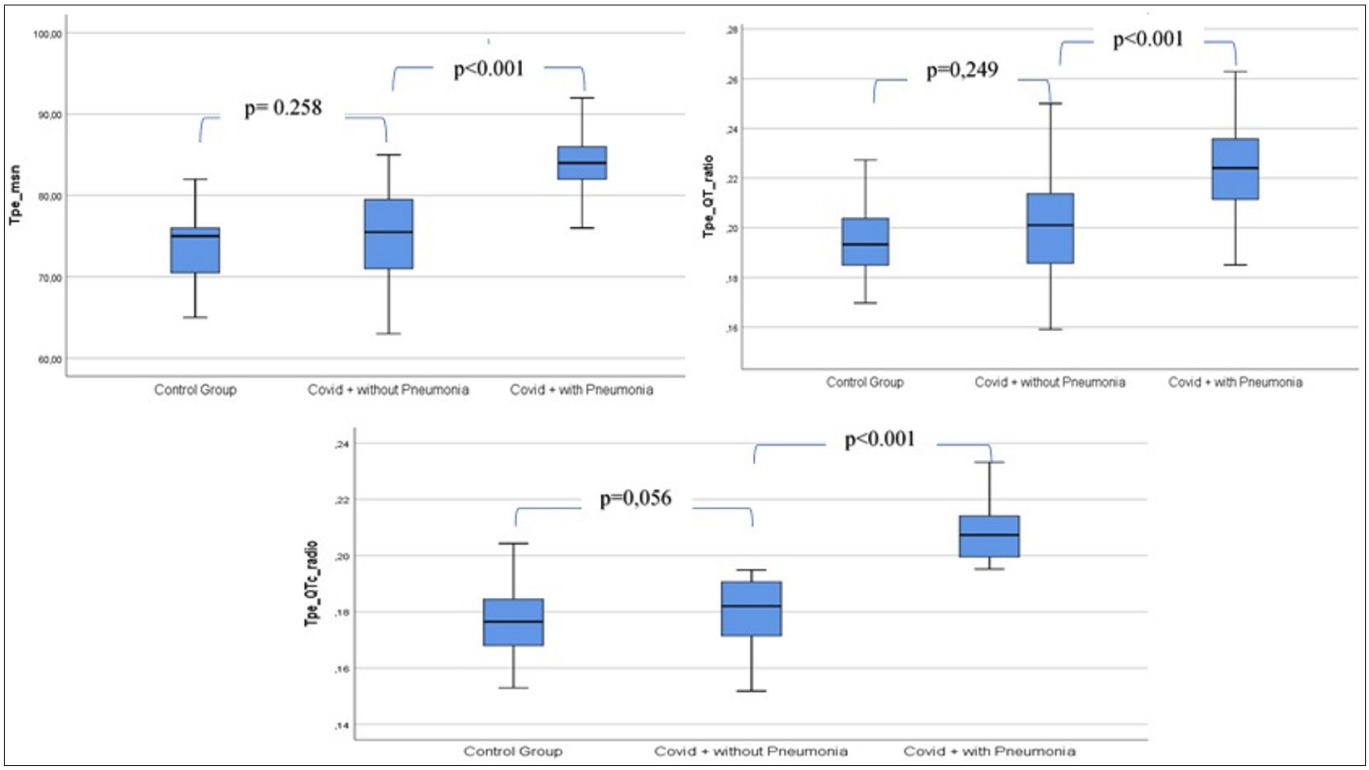

Figure 1. Change of Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio between study groups.

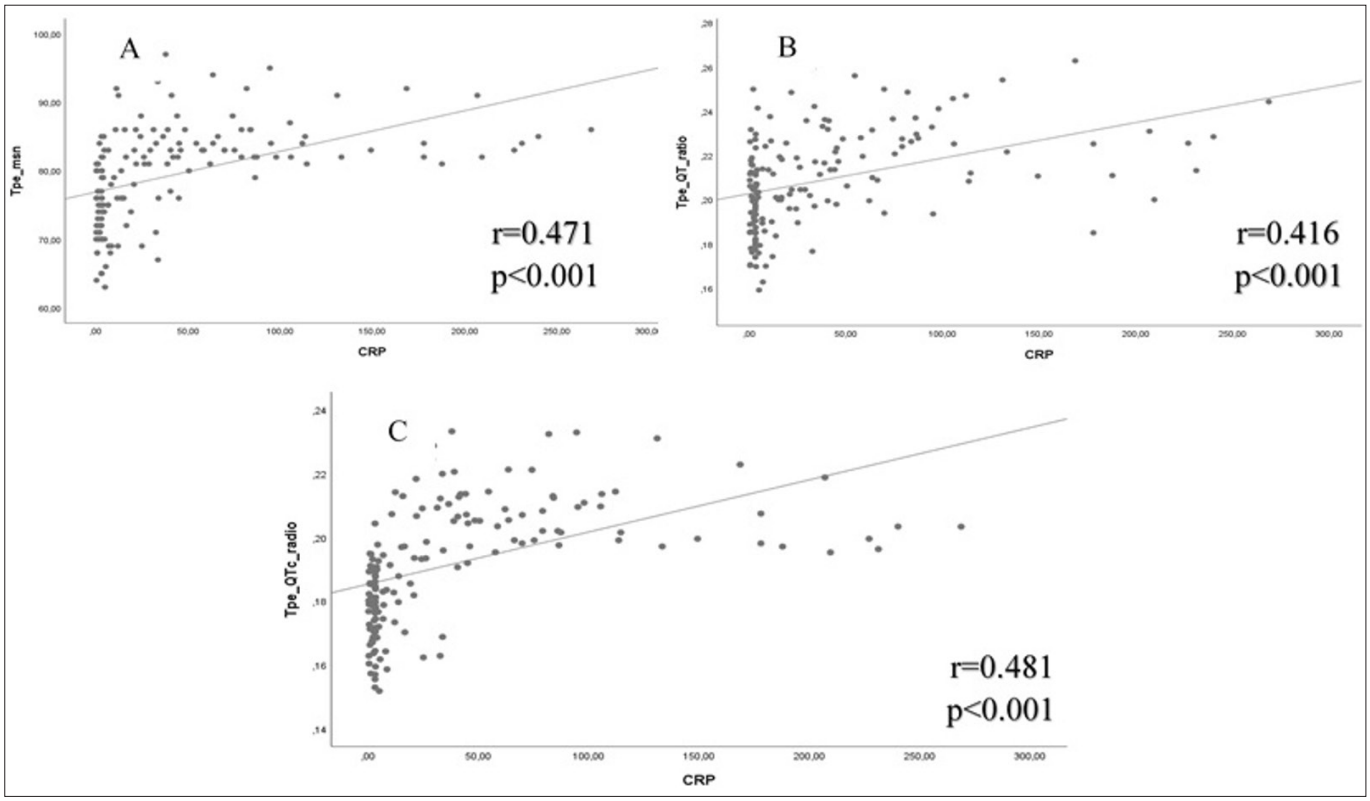

Figure 2. **(A)** Correlation between Tp-e interval and CRP count. **(B)** Correlation between Tp–e/QT ratio and CRP count. **(C)** Correlation between Tp–e/QTc ratio and CRP count

Shi et al. (15) from china reported that 16.7% of hospitalized COVID-19 patients and 44.4% of COVID-19 intensive care patients had malignant arrhythmias. Some 12-lead ECG parameters as potential markers of malignant arrhythmias have been proposed.

In a previous study, the QTc interval and QT dispersion which show myocardial repolarization status have been used for risk stratification in different patient groups (16). In recent years, the use of Tp-e interval and Tp-e/QTc ratio in determining ventricular arrhythmias and risk of sudden cardiac death has become increasingly common. Previous studies have claimed that the mechanism of association of prolonged QT interval, Tp-e interval, and sudden cardiac deaths is a tendency to ventricular re-entry which causes ventricular arrhythmias (17).

Because Tp-e/QTc ratio is not affected by alteration in heart rate and interpersonal variation of QT interval, the Tp-e/QTc ratio is a more useful parameter than Tp–e and QT intervals (13).

In our study found out that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios which are the most susceptible index of myocardial repolarization and which may show a higher tendency to ventricular arrhythmia and sudden cardiac death were meaningfully prolonged in COVID-19 patients with pneumonia. The same values are similar to healthy people in those who have mild disease despite having COVID-19. that is, we found that the probability of ventricular arrhythmia does not increase in this patient group. Therefore, the risk of ventricular arrhythmia in these individuals can be said to be similar to that of the healthy.

Hence, these results imply that the risk of development of arrhythmias is higher in COVID-19 infected patients with pneumonia. However, this status only was seen in patients who had experience pneumonia. What could the possible mechanisms behind the relationship we observed with COVID-19 infection in this study?

Although studies about cardiac damage and long-term effects of COVID-19 are very recent and uncertain, there is remaining, evidence that it can induce cardiac pathologies and/or exacerbate existing cardiovascular diseases. COVID-19, possible mechanisms involved in the physiopathology of cardiac injury are as follows: Direct cardiotoxic effect (myocarditis) through ACE2 receptor which plays an essential role in the pathogenesis of the virus, increased sympathetic stimulation, hypoxia due to lung involvement, productions of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α secondary to inflammation and increased clotting tendency could be the possible mechanisms (18).

Myocarditis can be seen in the course of the disease, although it is very rare (19). Huang et al. (20) demonstrated that COVID-19 linked with myocardial damage occurred in approximately 12.1% of patients and appeared as an increase in hs-TnI levels.

In a study by Ucar et al. (21) in patients with myocarditis,

they reported that there is a prolongation of the Tp-e interval and Tp-e/QT ratio due to local inflammation and fibrosis of the myocardium.

In our study, both because LVEF was normal in echocardiography and blood troponin I levels was normal has removed us from the diagnosis of possible myocarditis. For this reason, the change in the Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios index in our study is considered to be independent of myocarditis.

The mechanism of cardiac and arrhythmic complications may be associated with pro-inflammatory mediators which increase COVID-19 infection. Production of pro-inflammatory cytokines secondary to inflammation, such as IL-1β, IL-6, IL-18, and TNF-a, has been shown to increase in patients with severe COVID-19 infections by Madjid et al. (22).

In previous studies on transgenic mouse models, a strong relationship has been demonstrated between inflammation and pro-inflammatory cytokines (TNFα and IL-1β) and arrhythmia formation (23). Lagrand et al. (24) showed that CRP can cause direct arrhythmias by activating complement and inducing oxidative stress and apoptosis. CRP level which conventionally uses in infectious diseases is correlated with several cytokine levels such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNFα) levels (25). As known, local or circulating pro-inflammatory cytokines are correlated with plasma CRP levels. The greater the severity of the inflammatory stimulus, the greater the change in the concentrations of the acute phase proteins such as CRP. That is, CRP correlates with the extent and severity of the disease. Therefore, in our study a markedly increase in CRP levels in COVID-19 patients who have had pneumonia, suggests that these patients had a stronger inflammatory response. In light of these data, it can be concluded that the increase in CRP increases the incidence of arrhythmia. It can be said that these patients are more sensitive to ventricular arrhythmia because the inflammation increases the risk of arrhythmia in COVID-19 pneumonia patients. Moreover, this study demonstrated that the inflammatory marker CRP correlated with the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratios, positively. That's why it can be said that the risk of arrhythmia increases significantly due to the increase in the CRP level. Therefore, we can consider that this present study's results are similar to the previous results.

In COVID-19 patients without pneumonia, it can be thought that the CRP levels are significantly lower, resulting in a much less inflammatory response. The similarity of the risk of ventricular arrhythmia to healthy people in these patients can be explained by an insufficient inflammatory response. In this study.

Soto-Gomez et al. (26) found an increase in newly started arrhythmic events in patients hospitalized for pneumonia. So, they claimed that pneumonia is an arrhythmogenic disease. It has been shown by Restrepo et al. (27) that pneumonia affects the cardiovascular system with multiple mechanisms and causes cardiac arrhythmias. Similar results have been shown by Corrales-Medina et al. (28). Possible causes, according to them, can be listed as follows: increase in serum inflammatory cytokines, acute physiologic or metabolic disorders related to pneumonia, such as hypo/hyperthermia, electrolyte abnormalities, and hypoxemia, may trigger arrhythmias. The development of pneumonia in COVID-19 infected patients may have increased the risk of arrhythmia by the mentioned mechanisms. Therefore, it is reasonable that Tp-e, Tpe/QTc ratio values, which are an indicator of possible ventricular arrhythmia, are significantly prolonged in patients with pneumonia, as in our study. Also, in our study, the most important finding that supports these data is the correlation finding between inflammation parameters and Tp-e/QT ratio and Tp-e/QTc ratios index.

Öztürk et al. (29) claimed that QTc, QTd, and Tp-e/QTc, were significantly prolonged in COVID-19 patients. However, in this study, the number of patients is limited, and the severity of the disease is uncertain. In our study, we divided COVID-19 patients into 2 groups according to the presence or absence of pneumonia, which we think indicates the severity and viral load of the disease. In our study, we found that arrhythmia potential was present only in COVID-19 patients who developed pneumonia rather than all COVID-19 patients. This is the most crucial data of our study.

CONCLUSION

When the results obtained in our study are evaluated; abnormal dispersion of ventricular repolarization has existed in severe COVID-19 patients. Considering that the Tp-e interval and Tp-e/QTc ratio have been used as the electrocardiographic index of ventricular arrhythmogenesis and sudden cardiac death in recent years, COVID-19 patients with more serious diseases such as pneumonia have a high risk for cardiac arrhythmia and sudden cardiac death. We think that patients with COVID pneumonia should be followed more closely for ventricular arrhythmia, especially since the drugs used in the treatment of COVID 19 have the potential to affect ventricular repolarization parameters. Also, ECG can be used to evaluate the risk of cardiac arrhythmia in severe COVID-19. We also think that this work is a pilot study for future research of the Tp–e interval, the Tp–e/QTc ratio, and COVID-19 related arrhythmia and mortality.

Limitations

The main limitations of our study are the relatively small

number of patients in our study group to see if prolonged Tpe, Tpe/QTc ratio develop ventricular arrhythmias in COVID-19 patients and the lack of follow-up in terms of possible future ventricular arrhythmias.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by Kayseri City Hospital Clinical Research Ethics Committee (Date: 25.06.2020, Decision No: 135).

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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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. 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. doi: 10.1001/jama 2020. 2648.
2. Özdemir Ö. Coronavirus Disease 2019 (COVID-19): Diagnosis and Management. Erciyes Med J 2020; 42: 242-7.
3. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020; 116: 1666-87.
4. Kelesoglu S, Yilmaz Y, Ozkan E, et al. New onset atrial fibrilation and risk faktors in COVID-19. J Electrocardiol 2021; 65: 76-81.
5. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl) 2020; 133: 1025-31.
6. Elming H, Holm E, Jun L, et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J 1998; 19: 1391-400.
7. Tse G, Yan BP. Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death. Europace 2017; 19: 712-21.
8. Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol 2008; 41: 575-80
9. Castro Hevia J, Antzelevitch C, Tornes Barzaga F, et al. Tpeak-T end and T peak-T end dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006; 47: 1828-34.
10. T.C. Ministry of Health General Directorate of Public Health, COVID-19 (Sars-Cov2 Infection) Directory, Coronavirus Scientific Advisory Board, Turkey 2020
11. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019; 40: 237-69
12. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012; 33: 1635–701.
13. Gupta P, Patel C, Patel H, et al. Tp-e/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008; 41: 567-74.
14. Kors JA, van Herpen G, van Bemmel JH. QT dispersion as an attribute of T-loop morphology. Circulation 1999; 99: 1458-63.
15. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020; 5: 13–364.
16. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. The Lancet 1994; 343: 327-9.
17. Antzelevitch C, Sicouri S, Di Diego JM, et al. Does Tpeak–Tend provide an index of transmural dispersion of repolarization? Heart Rhythm 2007; 4: 1114-6.
18. Tomasz J. Guzik et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020.
19. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J 2020.
20. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506
21. Ucar FM, Ozturk C, Yılmaztepe MA. Evaluation of Tp-e Interval, Tp-e/QT Ratio and Tp-e/QTc Ratio in Patients with Acute Myocarditis. BMC Cardiovasc Disord 2019; 19: 232
22. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol 2020.
23. Brouillette J, Cyr S, Fiset C. Mechanisms of arrhythmia and sudden cardiac death in patients with HIV infection. Can J Cardiol 2019; 35: 310-9.
24. Lagrand WK, Visser CA, Hermens WT,et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 1999; 100: 96-102.
25. Kushner I. The phenomenon of the acute phase response. Ann New York Acad Sci 1982; 389: 39-48
26. Soto-Gomez N, Anzueto A, Waterer GW, Restrepo MI, Mortensen EM. Pneumonia: an arrhythmogenic disease? Am J Med 2013; 126: 43-8.
27. Restrepo MI, Reyes LF. Pneumonia as a cardiovascular disease. Respirology 2018; 23: 250-9.
28. Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. Lancet 2013; 381: 496–505.
29. Öztürk F, Karaduman M, Çoldur R, İncecik Ş, Güneş Y, Tuncer M. Interpretation of arrhythmogenic effects of COVID-19 disease through ECG. Aging Male 2020: 1-4.

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Relationship of socioeconomic status and oral-dental health in the Southeastern Anatolia

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ABSTRACT

Aim: Oral and dental health is affected by factors such as general health status, socioeconomic status.The aim of this study is to investigate the effects of socioeconomic status on DMFT and oral hygiene habits of patients.

Material and Method: 400 patients who applied to Dicle University Faculty of Dentistry Department of Restorative Dentistry for dental treatments were asked to fill in a questionnaire to reflect their oral hygiene habits along with their descriptive information and socioeconomic status. Clinical and radiological examinations of the patients were made, and the value of the DMFT index was determined for each patient. Statistical analysis was performed using Mann Whitney U and Chi-Square tests.

Results: According to our study, the education status, monthly income and frequency of tooth brushing affect the DMFT index value statistically significantly ($p<0.05$). Although 69.6% of those participating in the study are young people aged 35 and under, 46.3% do not work at any job; 84.2% of them can reach a monthly income of 4001 TL or less per month. In addition, 65.8% of the people participating in the survey think that their economic status affects oral and dental health. Those with the lowest monthly income have the highest DMFT confirms the opinion of the participants.

Conclusion: Based on the results of our study, in which we found that the disadvantaged socioeconomic situation had a negative impact on oral and dental health, we think that this situation can be improved with social state practices such as fluoride prophylaxis, distribution of oral hygiene equipment.

Keywords: Oral-dental health, socioeconomic status, DMFT

INTRODUCTION

Today, the different socioeconomic conditions of individuals have led to the idea that their access to health services and oral hygiene tools will not be equal.Living standards of different segments of society; changes according to criteria such as financial situation, place of residence, and this variability is also observed in the oral hygiene and treatment approaches of the patients. Neglected oral health can often cause tooth decay and gum disease, and if it continues, tooth loss. Dental caries causing conditions such as pain, aesthetics and loss of function, and the local effect, where the necessary treatments are not done on time, can turn into a systemic effect, which can deeply affect the general health, and this may rarely cause death (1-3). The prevalence of this situation has been found to be particularly high for socioeconomically disadvantaged groups (4).

Although oral-dental health is seen as a localized concept, many studies show that it is significantly associated with various systemic diseases (5,6). Good oral hygiene; is one of the main factors of maintaining oral health as well as general health (7).

Individuals have been reported to be healthier as their socioeconomic status increases (8). Although it is more prominent in groups such as women, children and the elderly, the effects of differences in socioeconomic status on health; plays a significant role in the health of the whole society. The socioeconomic status affects the knowledge and attitudes of the parents on the subject, therefore it is a determining factor for the positive or negative effect of the parents on the child (9).

The DMFT (Carious, missing and filled teeth) index is one of the common methods used for nearly 80 years to assess the prevalence of dental caries and dental treatment needs among populations in oral epidemiology (10). The DMFT index is based on a field clinical examination of individuals using an end, mirror, and cotton rolls, and

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is simply detects the number of decayed, missing and restored teeth. Another version proposed in 1931 is the carious, incomplete and filled surface (DMFS) index by counting each affected surface, DMFT, the most widely used dental index by WHO, can be made using the least material, effort and time. It is an index that is simple, easy to apply clinically and can be supported with panoramic x-rays, causing it to be used frequently.

The hypothesis of our study; Individuals with a high socioeconomic level will have better oral-dental health than those with low socioeconomic status; individuals with higher education level will have lower DMFT index values.

MATERIAL AND METHOD

Approval for the study was given by the Ethics Committee of Dicle University Faculty of Dentistry (Date: 27.01.2021, Decision No: 2021/07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

A questionnaire form was presented to a total of 400 patients who applied to Dicle University Faculty of Dentistry to evaluate the effect of their socioeconomic status on DMFT index values and oral hygiene habits with informed consent. Routine radiological and oral examinations of the patients were performed.

At the beginning of the form, there are questions describing the sociodemographic characteristics of the patients (age, gender, etc..). In the second part of the questionnaire, attitude and behavior evaluation questions such as oral hygiene habits of the patients and frequency of tooth brushing were asked. DMFT index values were also determined as a result of the clinical and radiological examinations of the patients; decayed teeth in the mouth, teeth restored with filling and lost teeth were calculated and included in the examination.

Statistical Analysis

After determining the socioeconomic status and oral hygiene habits, the relationship between the two parameters was evaluated statistically. Frequency distribution tables were created for general properties. Kolmogorov-Smirnov test was applied to determine the suitability of the DMFT index to normal distribution and p: 0.00; Since p <0.05, it was found that it did not show a normal distribution. In line with this result, the Mann Whithney U test was used to compare the DMFT index with the variables of 2 categories and the Kruskal-Wallis test for the comparison of the variables with more than 2 categories and the Chi square test for the comparison of the 2 categorical variables. The confidence interval is 95% and the significance value is 5%.

RESULTS

According to results; 41.8% were in the 18-25 age group, 27.8% in the 25-35 age group, 19.3% in the 35-45 age group, 7.8% in the 45-55 age group, and A total of 400 patients participated, 3.5 of whom were 55 years of age or older. 57.8% of the participants are women and 42.3% are men. The general distribution is shown in **Table 1** and **Table 2**.

Table 1. Distribution of sociodemographic characteristics of participants

	N	%
Age		
18-25	167	41.8
26-35	111	27.8
36-45	77	19.3
46-55	31	7.8
56 years and older	14	3.5
Gender		
Female	231	57.8
Male	169	42.3
Education		
Literate/primary school	76	19.0
Middle school	65	16.3
High school	133	33.3
University (undergraduate)	118	29.5
Postgraduate/doctorate	8	2.0
Profession		
Artisan	11	2.8
Officer	51	12.8
Worker	54	13.5
Unemployee	185	46.3
Other	99	24.8
Living Place		
Village	29	7.2
District	68	17.0
Province	303	75.8
Number of individuals in the family		
1-4	130	32.5
5-8	212	53.0
Over 8	58	14.5
Health assurance		
With	312	78.0
With out	88	22.0
Monthly income		
2000 TL and below	203	50.7
2001-4000 TL	134	33.5
4001-6000 TL	39	9.8
6001 TL and above	24	6.0
Total	**400**	**100**

The monthly income of 50.7% of the participants is 2000 TL and below, 33.5% 2001-4000 TL, 9.8% 4001-6000 TL and 6% 6001 TL and above. While 11.5% of the participants never go to the dentist, 68.8%, that is, the majority of them, when there is pain, 7% go every 6 months and 12.8% once a year. 80% of the individuals participating in the study think that oral and dental cleaning affects the general health. 56.3% of the participants use salty/carbonated water prepared at home as a mouthwash, and 43.8% use ready-made solutions.

Table 2. Findings on knowledge, attitudes and behaviors related to oral health and oral hygiene habits			
		N	**%**
Do you have any health problems?	Yes	44	11.0
	No	356	89.0
Is there any medication you use regularly?	Yes	37	9.3
	No	363	90.8
How often do you go to the dentist?	No	46	11.5
	When there is pain	275	68.8
	Every 6 months	28	7.0
	Once a year	51	12.8
Do you think oral and dental hygiene affect general health?	Yes	320	80.0
	No	78	19.5
How many times should teeth be brushed a day?	4 Times	13	3.3
	3 Times	125	31.3
	2 Times	208	52.0
	1 Time	51	12.8
	Not brushed	3	0.8
What is your brushing frequency?	2 times a day	201	50.2
	Once a day	134	33.5
	Rare	59	14.8
	I never brush	6	1.5
Which products do you use most for oral and dental cleaning?	Toothbrush/toothpaste	370	92.5
	Floss	8	2.0
	Mouthwash	6	1.5
	Toothpick	15	3.8
	Miswak	1	0.3
Do you think toothpaste brand affects oral hygiene?	Yes	300	75.0
	No	100	25.0
Do you think toothpastes/toothbrushes are expensive?	Yes	260	65.0
	No	140	35.0
Do you think dental cleaning products (dental floss, interface brush, mouthwash, etc.) are expensive?	Yes	271	67.8
	No	129	32.3
Which one do you use as a mouthwash?	Homemade salted/carbonated water	225	56.3
	Ready-made mouthwash solutions	175	43.8
Do you think dental treatments are expensive?	Yes	343	85.8
	No	57	14.2
What is your smoking frequency?	I don't use	275	68.8
	Less than 1pack per day	84	21.0
	1 package per day	34	8.5
	More than1packper day	7	1.8
Do you think dental treatment costs (dental filling, tooth extraction, prosthesis, implant, etc.) can be avoided by cleaning the mouth?	Yes	201	50.2
	No	199	49.8
Do you think your economic situation affects your oral and dental health?	Yes	263	65.8
	No	137	34.3
Have you received oral and dental health training from your mother/father as a child?	Yes i got	181	45.3
	No i didn't get	219	54.8
Did your parents have a habit of brushing teeth?	Yes	226	56.5
	No	174	43.5
Total		**400**	**100**

75% of the respondents think that the toothpaste brand affects oral hygiene and 65% think that toothpaste and brushes are expensive. 67.8% of the participants stated that dental cleaning products (dental floss, interface brush, mouthwash, etc.) are expensive. The majority of the participants (85.8%) think that dental treatments are expensive. 50.2% think that dental treatment (dental filling, tooth extraction, prosthesis, implant, etc.) costs can be avoided by cleaning the mouth. 65.8% of the participants think that their economic conditions affect their oral and dental health.

There is a statistically significant difference between the educational status of the participants and their

Table 3. DMFT index values analysis table

	Rank averages	X2/z	P
Education		13.832	0.008
Literate/primary school	232.12		
Middle school	208.82		
High school	205.14		
University (undergraduate)	172.50		
Postgraduate/doctorate	168.38		
Monthly income		14.026	0.003
2000 TL and below	207.67		
2001-4000 TL	204.57		
4001-6000 TL	201.59		
6001 TL and above	115.35		
Living place		0.025	0.988
Village	197.98		
District	199.45		
Province	200.98		
How often do you go to the dentist?		6.966	0.073
No	178.41		
When there is pain	209.13		
Every 6 months	207.98		
Once a year	169.75		
What is your brushing frequency?		8.187	0.042
2 times a day	194.59		
Once a day	191.30		
Rare	236.87		
I never brush	246.25		
Have you received oral and dental health training from your mother/father as a child?		21.124	0.256
Yes, i got	193.29		
No,i didn't get	206.46		

DMFT index ($p<0.05$). Participants whose educational background is literate/primary school have the highest DMFT index and the participants with graduate education have the lowest.

There is a statistically significant difference between the monthly income of the participants and their DMFT index ($p<0.05$). Participants with a monthly income of TL 2000 and below have the highest DMFT index values, whereas participants with a monthly income of 6001 TL and above have the lowest values.

There is a statistically significant difference between the frequency of brushing of the participants and their DMFT index ($p<0.05$). Participants who never brush their teeth had the highest DMFT index values and those who brushed once a day had the lowest DMFT index values.

No significant relationship was found between the monthly income and the type of mouth/teeth cleaning products they use the most and also, between monthly income and the situation of thinking that dental treatments are expensive as a continuation of toothpaste and brushes, dental cleaning products ($p> 0.05$). There is a statistically significant difference between the opinions of the participants about the required frequency of brushing and their parents having a habit of brushing their teeth ($p <0.05$).

This situation is shown in **Table 4** and **Table 5**.

Table 4. Relationship between monthly income and access to oral hygiene tools

		Monthly income				X2	P
		2000 TL and below	2001-4000 TL	4001-6000 TL	6001 TL and above		
Which products do you use most for oral and dental cleaning?	Toothbrush/toothpaste	186(91.6%)	123(91.8%)	37 (94.9)	24 (100%)	6.925	0.863
	Floss	4 (2%)	3 (2.2%)	1 (2.6%)	0		
	Mouthwash	4 (2%)	2 (1.5%)	0	0		
	Toothpick	8 (3.9%)	6 (4.5%)	1 (2.6%)	0		
	Miswak	1 (0.5%)	0	0	0		
Do you think toothpastes/toothbrushes are expensive?	Yes	127 62.6%)	87 (64.9%)	30 (76.9%)	16 (66.7%)	2.997	0.392
	No	76 (37.4%)	47 (35.1%)	9 (23.1%)	8 (33.3%)		
Do you think dental cleaning products (dental floss, interface brush, mouthwash, etc.) are expensive?	Yes	133(65.5%)	91 (67.9%)	30 (76.9%)	17 (70.8%)	2.071	0.558
	No	70 (34.5%)	43 (32.1%)	9 (23.1%)	7 (29.2%)		
Do you think dental treatments are expensive?	Yes	176(86.7%)	114(85.1%)	34 (87.2%)	19 (79.2%)	1.116	0.773
	No	27 (13.3%)	20 (14.9%)	5 (12.8%)	5 (20.8%)		
Do you think your economic situation affects your oral and dental health?	Yes	131(64.5%)	89 (66.4%)	28 (71.8%)	15 (62.5%)	0.906	0.824
	No	72 (35.5%)	45 (33.6%)	11 (28.2%)	9 (37.5%)		

Table 5. The relationship between toothbrushing knowledge level and parental behavior

		How many times should teeth be brushed a day?					X2	p
		4 times	3 times	2 times	1 time	Not brushed		
Have you received oral and dental health training from your mother/father as a child?	Yes, i got	4(2.2%)	65(35.9%)	92 (50.8%)	20 (11%)	0	6.715	0.152
	No, i didn't get	9(4.1%)	60(27.4%)	116 (53%)	31 (14.2%)	3 (1.4%)		
Did your parents have a habit of brushing teeth?	Yes	6 (2.7%)	80 (35.4%)	117(51.8%)	23 (10.2%)	0	10.027	0.040
	No	7 (4%)	45 (25.9%)	91 (52.3%)	28 (16.1%)	3 (0.8%)		

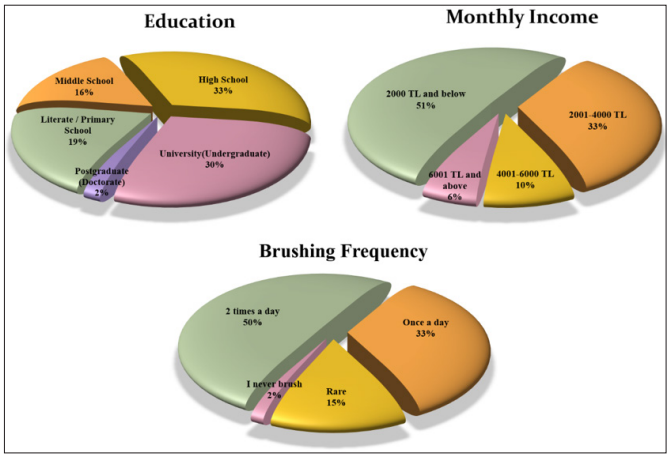

Figure.

DISCUSSION

Socioeconomic conditions of societies also change with the change of living conditions. Socioeconomic status, which is a multi-factor concept; It is effective in all areas of life, factors such as monthly income and education level of individuals affect their access to health equipment and services, and the quality of the health service they receive.

In this study, by determining the socioeconomic conditions and oral health conditions of the patients who applied to Dicle University Faculty of Dentistry; Oral and dental health habits, access to oral hygiene tools and attitudes, behaviors and thoughts on the subject were evaluated.

Although the effects of social inequalities on oral health are observed in studies on human societies, it is difficult to evaluate the impact of socioeconomic differences in all aspects (11,12). Therefore, much more and detailed examination is required in order to have an idea about the impact of socioeconomic variables.

In the health model they developed Whitehead and Dahlgren (13) define healthy lifestyle behaviors as a result of the socioeconomic environment beyond being an individual preference. In our study, the majority of the participants think that their economic conditions affect their oral and dental health, and their oral health status also affects their general health.

Rupasree et al. (14) concluded that there is a strong correlation between lifestyle, education level and socioeconomic status and periodontal diseases. Among the participants in our study, those who were literate/ primary school staining compared to the other groups with the highest level of DMFT index knowledge. However, the low DMFT index value suggests that graduate students have an effect on teeth.

Astrom et al. (15) stated in their study that individuals belonging to higher income groups had lower rates of reporting toothache and were more likely to be satisfied with their oral and dental health status than those in the lower socioeconomic group. In addition to the positive correlation between monthly income and DMFT, we think that education level, which is one of the factors that can provide higher socioeconomic opportunities, may also be effective in this issue.

Wennstrom et al. (16) conducted a study on trends in tooth loss in Swedish women and observed that women in lower socioeconomic groups tend to have fewer teeth, regardless of their age. This study shows that monthly income is an important factor on the DMFT value, as in our study, and our study supports the literature in this respect.

Tooth brushing is the main mechanical method of plaque elimination and therefore has been shown to reduce the risk of developing dental diseases. It should be kept in mind that dental caries and periodontal diseases, which are diseases that can be prevented by regular tooth brushing, may cause tooth loss, and this will increase the rate of missing teeth scored in the DMFT index (17).

Yadav conducted a study on his brushing habit and stated that his elders had never used toothbrushes until that day and instead used Neem and Babool branches. In our study, 92.5% of the participants stated that they mostly used toothbrush/toothpaste for cleaning their mouth and teeth, while the rate of those who stated that they used the natural tree branch, miswak, remained at 0.3%. This situation may suggest that the region and cultural factors are also effective on oral and dental health.

Again, Yadav's next focus (18) was the price of toothbrushes purchased by consumers, the economic situation; assessed the effect of individuals on access to oral and dental health supplies. Most of the consumers stated that they prefer to buy toothbrushes in promotional packages such as "buy two instead of one" in order to get extra profit, and that economic factors are effective in their choice of brushes. The findings support our findings in that individuals find oral dental health products expensive and monthly income affects their brushing habits.

Agata et al. (19) suggesting that individuals who have visited a dentist in the last 3 months and brushed their teeth 3 times a day have less chronic kidney disease, hypertension or diabetes, most of the hemodialized patients had an appointment with a dentist at the earliest one year before filling out the questionnaire, or what was the last They stated that they did not remember that they had time appointments. This result may show the effect of general health on oral and dental health. The vast majority of the individuals in our study also think that oral and dental hygiene affects their general health.

Gaurav et al. (20) reported that the use of even tongue cleaner was significantly higher in the upper middle

socioeconomic class patients, whereas the majority (81.3%) of the individuals in the lower socioeconomic class did not go to a dentist at all. The result of this study, which states that monthly income and economic level affect oral hygiene habits and accessibility, is also in line with our findings.

Singh et al. (21) in a study conducted among adults, showed that individuals in lower socioeconomic positions tend to cluster to a higher degree of multiple risk factors for worse oral and dental hygiene than those in higher socioeconomic positions. Here, it can be shown that individuals with a high economic level can purchase oral hygiene products and the frequency of going to the dentist for controls creates less economic problems.

Hooley et al. (22) suggests that people from socioeconomic classes considered higher develop tooth decay at a slower rate than people with low socioeconomic status, due to a more tooth-friendly diet and increased access to fluoride. In our study, the rate of those who can reach fluoride-containing mouthwash cannot even reach half of the participants. We think that this situation is related not only to financial situation but also to the level of oral hygiene awareness.

Elger et al. (23) in their study concluded that oral dental health was affected by socioeconomic status. It has been suggested that diets that cause obesity are seen more in those with a high socioeconomic level and this may cause a high DMFT level. Environmental factors such as the place of residence, economic factors such as monthly income, or personal factors such as obesity are also determinants. However, it is stated that regular tooth brushing is the primary factor in the prevention of caries.

Rani et al. (24) found that children who don't use toothbrushes have a higher rate of tooth decay , they reported that the children of families with good socioeconomic status were more likely to brush their teeth.

Salamaa et al. (25) argued that socioeconomic status has an effect on the knowledge, attitudes and practices of parents and may affect their children's health status in general and oral health in particular, depending on the level of parental care. However, regarding the oral hygiene status of the children (the number of filled and decayed teeth), it showed that there was a statistically significant difference between the number of filled and decayed teeth, which was related to the mothers' level of knowledge. In our study, almost half of the participants answered positively to the question of "Did you receive oral dental health education from your parents as a child", but in paired comparisons, this situation did not have a significant effect on their opinions about the number of daily brushing teeth required.

Tooth decay, as a multifactorial disease, follows a chronic process that is also affected by environmental factors and cultural factors. It is a generally accepted inference that mothers' knowledge of oral hygiene, attitudes and behaviors supportive of oral hygiene also affect the dental health of children. However, in our study, no statistically significant difference was found between the oral and dental health education/DMFT value received from the mother/father. Bali et al. showed that children in the higher socioeconomic group were at a lower risk of caries. However, it has been reported that children from families with lower socioeconomic status are at greater risk for the development of dental caries, in line with the literature (26,27). In our study, the DMFT indexes of participants with a monthly income of 2000 TL or less were found to be the highest, however. The DMFT index of the participants with a monthly income of 6001 TL and above was found to be the lowest and it was thought that the economic situation could be more effective on oral health than thought.

Marchesan et al. In their study conducted in 2020, they evaluated the relationship between dental floss use and oral diseases among the elderly, and as a result of a 5-year observation and follow-up, they found that people using dental floss had less periodontitis, caries and tooth loss. In our study, 60% to 70% of participants in all income groups reported that they found oral hygiene tools, including dental floss, expensive. It is ignored that a small amount of floss can clean the whole mouth, and a box of floss can be used for a long time. Majority of the participants defined the hygiene tool they use the most as a toothbrush/paste, and a very small portion stated that they used dental floss more. We think that this is a result of the perception of the cost of flossing as well as the idea of applying flossing to all interdental areas one by one, causing laziness (28).

On the other hand, Neamatollahi and Ebrahimi (29) reported that doctoral and graduate students tend to use dental floss more frequently than undergraduate students. The study conducted supports the significant relationship we found between education and DMFT.

Oral and dental health problems are seen as a common public health problem, and socioeconomic factors are also effective according to research findings. The H0 hypothesis is that socio-economic status has no effect on community oral and dental health. And The H0 hypothesis was rejected according to the results of our study, in which we found that the disadvantaged socioeconomic situation had a negative effect on oral and dental health. We are of the opinion that the problem can be solved by addressing all its dimensions through improvements in health insurance and social state policies.

CONCLUSION

In the light of the data obtained in our study, it can be mentioned that there is a positive correlation between the educational status and monthly income of the individuals and their brushing habits. Patients who think that the price of toothpaste/toothbrush, which is the basic oral hygiene tool, is expensive, also think that dental treatments are expensive and their socioeconomic status affects their oral and dental health. Since this point of view is expensive, it can lead to avoidance of toothbrush/paste use, decrease in dentist visits and eventually deterioration of oral health.

With the improvements to be made regarding the social situation, economic conditions, the quality and content of education, the oral and dental health of individuals can be protected and access to health services and tools, one of the basic human rights, can be provided.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was given by the Ethics Committee of Dicle University Faculty of Dentistry (Date: 27.01.2021, Decision No: 2021/07).

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. Broadbent ve diğerleri, 2008] (Broadbent JM, Thomson WM, Poulton R: Trajectory patterns of dental caries experience in the permanent dentition to the fourth decade of life. J Dent Res 2008; 87: 69–72.
2. Glockmann E, Panzner K, Huhn P, Sigusch B, Glockmann K. Ursachen des Zahnverlustes in Deutschland—Dokumentation einer bundesweiten Erhebung (2007) [Reasons for tooth loss in Germany—documentation of a nationwide survey (2007)]. Köln (Germany): IDZ-Information, Institute of German Dentists (IDZ) 2011
3. WHO. Non-Communicable Diseases and Their Risk Factors, 2018. Available at: https: //www.who.int/news-room/fact-sheets/detail/oral-healt. [accessed September 24, 2018].
4. Antunes J, Frazão P, Narvai P, Bispo C, Pegoretti T. Geographic Information Systems (GIS) in assessing dental health. Int J Environ Res Public Health 2010; 7: 2423–36.
5. Jin LJ, Lamster IB, Greenspan JS, Pitts NB, Scully C, Warnakulasuriya S. Global burden of oral diseases: Emerging concepts, management and interplay with systemic health. Oral Dis 2016; 22: 609-19.
6. Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: Review of the evidence. J Clin Periodontol 2013; 40: 8-19.
7. Park J.B, Han K, Park YG, Ko Y. Association between socioeconomic status and oral health behaviors: The 2008-2010 Korea national health and nutrition examination survey. Exp Ther Med 2016; 12: 2657-64.
8. Matthews KA, Gallo LC. Psychological perspectives on pathways linking socioeconomic status and physical health. Annu Rev Psychol 2011; 62: 501–30.
9. Kumar N, Gupta N, Kishore J. Kuppuswamy's socioeconomic scale: Updating income ranges for the year 2012. Indian J Public Health 2012; 56: 103–4.
10. Broadbent JM, Thomson WM. For debate: problems with the DMF index pertinent to dental caries data analysis. Community Dent Oral Epidemiol 2005; 33: 400-9.
11. Steele J, Shen J, Tsakos G, et al. The Interplay between Socioeconomic Inequalities and Clinical Oral Health. J Dent Res 2015; 94: 19–26.
12. Thomson WM: Social inequality in oral health. Community Dent Oral Epidemiol 2012; 40: S28–S32.
13. Ireland Capital & Health Survey. (2000). A Report on the allIreland capital & health survey: Inequalities in perceived health. Erişim: 28.01.2006. http: //www.publichealth.ie
14. Rupasree Gundala, Vijay K. Chava. Effect of lifestyle, education and socioeconomic status on periodontal health: Contemp Clin Dent 2010; 1: 23–6.
15. Astrom AN, Haugejorden O, Skaret E, Trovik TA, Klock KS. Oral Impacts on daily performance in norwegian adults: The influence of age, number of missing teeth, and socio-demographic factors. Eur J Oral Sci 2006; 114: 115–21.
16. Wennstrom A, Ahlqwist M, Stenman U, Bjorkelund C, Hakeberg M. Trends in tooth loss in relation to socio-economic status among Swedish women, aged 38 and 50 years: Repeated cross-sectional surveys 1968-2004. BMC Oral Health 2013; 13: 632013.
17. Daly, GC. Prescribing good oral hygiene for adults. Aust Prescr, 2009 Jun; 32: 72-5. Available from: http: //www.australianprescriber.com/magazine/32/3/72/5/.
18. Komal Yadav K. Consumer behaviour in relation to toothbrush marketing: a study on Jaipur District 2015 AIJRA Vol.II Issue III. ISSN 2455-5967.
19. Trzcionka A, Twardawa H, Mocny-Pachońska K, Tanasiewicz M. Oral cavity status of long-term hemodialized patients vs. their socio-economic status. Med Pr 2020; 71: 279-88.
20. Sharma G, Oberoi SS, Oberoi A. A cross-sectional survey to assess the effect of socioeconomic status on the oral hygiene habits J Indian Soc Periodontal 2016; 20: 531–42.
21. Singh A, Rouxel P, Watt R.G and Tsakos G: Social inequalities in clustering of oral health related behaviors in a national sample of British adults. Prev Med 2013; 57: 102–6.
22. Hooley M, Skouteris H, Boganin C, Satur J, Kilpatrick N. Body mass index and dental caries in children and adolescents: a systematic review of literature published 2004 to 2011. Syst Rev 2012; 1: e1520.
23. Elger W, Kiess W, Körner A, Schrock A, Vogel M, Hirsch C. Influence of overweight/obesity, socioeconomic status, and oral hygiene on caries in primary dentition. J Investig Clin Dent 2019; 10: e12394.
24. Rani S, Singh A, Virdi MS, Mehta LK. Impact of socioeconomic status on oral health and oral health practices among preschool children. J Adv Med Dent Sci Res 2017; 5.

25. Salama Aml A, Konsowa Eslam M, Alkalash Safa H. Mothers' knowledge, attitude, and practice regarding their primary school children's oral hygiene. Menoufia Med J 2020; 33: 11–7.
26. Bali RK, Mathur VB, Talwar PP, Chanana HB. National Oral Health Survey and Fluoride Mapping 2002-2003 India. 1st ed. New Delhi: Dental Council of India and Ministry of Health and Family Welfare, Government of India; 2004.
27. Touger-Decker R, Mobley C. Academy of Nutrition and Dietetics. Position of the Academy of Nutrition and Dietetics: Oral health and nutrition. J Acad Nutr Diet 2013; 113: 693–701.
28. Marchesan JT, Byrd KM, Moss K, et al. Flossing is associated with improved oral health in older adults. J Dent Res 2020; 99: 1047–53.
29. Neamatollahi H, Ebrahimi M. Oral health behavior and its determinants in a group of Iranian students. Indian J Dent Res 2010; 21: 84-8.

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Retrospective analysis of ovarian torsion incidence in 5186 women undergoing controlled ovarian hyperstimulation

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ABSTRACT

Aim: Ovarian torsion (OT) is one of the common gynecologic emergencies in reproductive age women. In our study, it is aimed to make a retrospective evaluation of OT cases developed after controlled ovarian stimulation (COH) for in vitro fertilization (IVF) treatment.

Material and Method: This retrospective study was carried out in an IVF clinic between January 2015- December 2020 . Ten cases who definitely diagnosed as OT were included in this study. The medical records of these patients were examined. Data were analyzed according to demographic, clinicopathological, and sonographic findings.

Results: Ten of 5186 IVF patients developed OT (10/5186; 0.19%) and all OT cases were PCOS. The mean age of OT patients was 27.3±4.1years and the mean body mass index (BMI) was 23.5±6.2 kg/m² respectively. The mean number of retrieved oocytes was 21.46±4.12. The average diameter of the twisted ovaries of patients was 121.4±56.1 mm. Laparoscopy was performed in all OT patients for detorsion of the ovaries. It was found that OT occurred more frequently on the right side (8/10; 80%).

Conclusion: OT is more common in cases with polycystic ovary syndrome (PCOS). The risk of OT is reduced by decreasing gonadotropin dosage as well as retrieved number of oocyte. Also, prefering frozen-thawed embryo transfer can decrease OT risk in PCOS patients.

Keywords: Ovarian torsion, in vitro fertilization, polycystic ovary syndrome

INTRODUCTION

In vitro fertilization (IVF) is a sequence of steps which starts with controlled ovarian hyperstimulation (COH) which is provided by exogenous gonadotropins (1). Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive-aged women and IVF is also performed in PCOS patients resistant to all other alternative treatments. The aim of COH is to obtain as many good quality oocytes as possible (2). The ideal stimulation regimen for IVF should have minimal side effects, the lowest cycle cancellation rates, the least drug cost, easy monitoring, and single pregnancy should be achieved ultimately (3). Ovarian reserve should be clearly evaluated in every woman in whom IVF is planned. The number of antral follicles and Anti-müllerian hormone (AMH) levels are two important factors for determination of gonadotropine regimen. Applying the same protocol for each case limits the success of the treatment. The development of acute abdominal pelvic pain shortly after assisted fertility treatment is often attributed to hyperstimulation of the ovaries. Ovarian torsion (OT) is one of the most common gynecologic emergencies in reproductive age women. The prevalence is 2–3% of all gynecological emergencies and it is the fifth most common surgical emergency (4). OT progresses with impaired circulation of ovarian peduncle by circling around its own axis incompletely or completely. Similar to other vascular pathologies, reduced venous return, extension of the ovaries, interstitial haemorrhage and oedema occur in in OTs. Partial ovarian rupture, ischemia and necrosis with subsequent arterial flow deterioration are observed. Diagnosis and treatment may be delayed because clinical findings in this process are nonspecific findings such as sudden abdominal pain, nausea, vomiting, leucocytosis, and fever (5,6). Various methods such as inflammatory markers, grey scale ultrasonography, Doppler ultrasonography and tomography are used

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to help in the diagnosis of OT. However, diagnosing accurately is often difficult due to nonspecific findings (7,8). An increase in the number of white blood cells (WBC) is frequently used clinically as an indicator of inflammation, and some studies have also presented that there was an increase in the number of WBCs in cases of OT (9). Furthermore, many inflammation-based scoring systems such as thrombocyte-lymphocyte ratio, prognostic nutritional index and neutrophil-lymphocyte ratio (NLR) have been used to predict the prognosis of inflammatory diseases (10). The final diagnosis of torsion is made by direct observation of the rotated ovary or adnexa with laparoscopy or laparotomy. Diagnostic values of clinical findings and laboratory tests are limited. Therefore, partial or complete loss of function of ovarian tissue may be caused in case of any delayed or incorrect diagnosis (11). The aim of this study is to evaluate women developing OT after COH for IVF treatment.

MATERIAL AND METHOD

The study was approved by the Ethical Committee of Beykoz University (Date: 21/12/2020, Decision No: 2020/4). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective case-control study was carried out in an IVF clinic between January 2015- December 2020 . The medical records of 5186 IVF patients were examined and 1207 of these patients were PCOS. Ten cases who definitely diagnosed as OT were evaluated in this study. All OT patients were PCOS resistant to other treatments. None of the patients were pregnant because we prefer frozen-thawed embryo transfer in all PCOS patients to decrease ovarian hyperstimulation syndrome (OHSS) risk. Our OHSS prevalence is less than 1% because of all freze strategy and analog trigger use. More than 20 oocytes were retrieved in 8 of 10 OT cases. None of the OT cases had ovarian cysts or OT history before COH treatment. We followed up the patients till the start of third menstrual cycleLaparoscopy was performed in all cases for treatment and we didn't perform ooferectomy in any cases and they were treated conservatively with ovarian detorsion. All patients were discharged at post-operative second day without any complication.

Data were analyzed according to demographic, clinicopathological, and sonographic findings. The patients were informed that previous patient files would be used during the research. They were free to be enrolled and leave the study at any time, and there would not be any research expense claimed to the family or social security institution, and individual information would be kept confidential.

Stimulation Protocol

In all PCOS patients, the COH were performed using the GnRH antagonist (Cetrotide, 0.25 mg, Merck Serono, İstanbul, Turkey) with a combination of rFSH (Gonal-F, Merck Serono, İstanbul, Turkey) and ovulation induction with GnRHa (0.2 mg, GonapeptylVR , Ferring Pharmaceuticals Ltd., Mumbai, India) . Oocyte collection was performed 35-36 hours after the ovulation induction. The vitrification of blastocysts were performed using the Cryotop method, as described by the manufacturer (Kitazato, BioPharma Co. Ltd., Fuji, Japan).

Statistical Analysis

The statistical data analysis was conducted through SPSS (Statistical Package for the Social Sciences) 23.0 package program(SPSS Inc., Chicago, IL, USA). The categorical measurements were summarized as numbers and percentages. Continuous measurements, on the other hand, were summarized as mean and standard deviation (median and minimum-maximum when needed).

RESULTS

Ten of 5186 IVF patients had OT (10/5186; 0.19%) and all OT cases were PCOS. The mean age of OT patients was 27.3±4.1 years and the mean body mass index (BMI) was 23.5±6.2 kg/m² respectively. The mean number of retrieved oocytes was 21.46±4.12. The average diameter of the twisted ovaries of patients was 121.4±56.1 mm. Laparoscopy was performed in all OT patients for detorsion of the ovaries. It was found that OT occurred more frequently on the right side (8/10;80%). Ovarian edema, abnormal adnexal positions, free fluid in the pouch, and absence/decreased blood flow in the ovary, occurred in 3, 5, 10, and 4 cases, respectively. The period between oocyte pick-up(OPU) and OT changed between 2-10 days. **Table** shown complete blood count features of cases . It was determined as a result of analysis that mean Red distrubution width (RDW) value of the patients was 15.3±6.5% and platelet distribution width (PDW) values were determined as 15.9±2.7 fL while mean platelet volume (MPV) values were 8.0±1.1 fL. It was also determined that the neutrophil levels of the patients were 10.9±3.2% and the lymphocyte levels were 1.4±0.7%. The mean Neutrophile lymphocyte ratio (NLR) value of the patients who were included in the study was found to be 11±8.2.

Table. Complete blood count features of cases

	Mean±SD	Mdn (Min-Max)
WBC(×1000/mL)	13100.4 ± 3270.1	12500 (7800-21000)
RDW (%)	15.3±6.5	13.9 (12.1-39,2)
PDW (fL)	15.9±2.7	16.6 (6.2-17.2)
Neutrophile (%)	10.9±3.2	11.4 (6.1-17.3)
Lymphocyte (%)	1.4±0.7	1.2 (0.5-3.2)
NLR	11.0±8.2	7.1 (3.6-29.6)
MPV (fL)	8.0±1.1	7.8 (6.6-10.1)

WBC:White blood cell , RDW: Red distrubution width, PDW: platelet distribution width , NLR :Neutrophile lymphocyte ratio) , MPV: Mean platelet volume

DISCUSSION

We found increased risk of OT in PCOS patients undergoing IVF treatment. Ovarian stimulation is the predisposing factor for OT by increasing the ovarian weight and volume. OT should be suspected and excluded in any woman who has undergone COH for IVF and admits with a complaint of severe abdominal pain. Any delay in diagnosis and treatment may cause ovarian ischemic necrosis (12). Symptoms are nonspecific, and there may be severe and localized right or left lower abdominal pain and palpable bulk and peritoneal findings can be faced with. According to Shadinger et al. (13) all patients (100%) had abdominal pain as the main symptom, while 85% of them had vomiting, 56% of them had leucocytosis, and 18% had a recorded fever. Also, in our patients the only consistent symptom was abdominal pain which is localized in the lower abdominal quadrant. Similar to Sahlu's (14) study the age of the OT patients was between 23-31 years. Laboratory tests which are requested at the diagnosis stage should include a complete blood count (CBC) and a complete metabolic panel. If the torsion is causing bleeding and inflammation, CBC may indicate anemia or leucocytosis as a response. These laboratory abnormalities are not specific and the laboratory values will appear normal in torsion most of the time (15). In our cases there was no anemia but 7 (70%) of the cases had leucocytosis. In a study, the increase in the leucocyte count of patients who were diagnosed with adnexal torsion was found to be 36.5-64% (15). Eriç et al. (16) found in their study that the leucocyte count was found to be significantly higher in patients with ovarian torsion than the patients in the other groups. NLR is studied as a biomarker in cardiovascular diseases, malignancy, diabetes, hypertension, autoimmune diseases, gynaecology and obstetric diseases (17-20) Soysal et al. (21) conducted a study and presented that NLR can be used in the discrimination of preoperative ovarian cysts and torsion, but it has no diagnostic value in discriminating ovarian cyst rupture and torsion. It was found in a study by Eriç et al. (16) that the NLR values in the group with OT were found to be significantly higher than the other groups. Similarly to this study, we also found high NLR value (11.0±8.2) in our study. Despite the studies emphasizing that the increase in MPV and RDW expansion in inflammatory cases such as acute appendicitis, there are also some other studies pointing that there is no relationship between adnexal torsion and MPV (21). A study which was carried out by Eriç et al. (16) revealed that there was no difference between groups according to RDW and MPV.In our study, the mean RDW was 15.3±6.5% while the mean MPV was found to be 8.0±1.1. In agreement with previous results, we found that OT occurred more frequently on the right side (8/10; 80%) (22,23).

Because right infundibulopelvic ligament is longer than the left one and the descending colon has a protective nature on the left side .The frequency of OT is increased in women undergoing ovulation induction with gonadotropins, especially in those with OHSS. Three studies determined the incidence of OT after IVF to be 0.08–0.13% (24-26). A few case reports of OT associated with PCOS have been reported, but the correlation between PCOS and OT is not strongly shown (27,28). But in our study all of the 10 cases were PCOS. This might be due to the increased size of the ovary, and resulting hypermobility of ovaries during COH. . Enlarged cystic ovaries because of ovarian stimulation, especially when complicated by OHSS, may predispose ovaries to torsion (29-31). When patients conceive after COH and in the setting of OHSS, the ovarian cysts persist and this increases the risk of an OT (26). Mashiach et al. (31) (1990), investigating 201 ovarian stimulation cycles complicated by OHSS, found 15 (7.5%) patients to have the complication of unilateral OT. In contrast to this study,OT risk is very low in our patient group (0.19%) because of widely used freeze-all strategy. Similarly,in a study conducted by Berkkanoğlu et al. (32) OT risk was low in freeze-all group.

We didn't perform oopherectomy in any cases and there was no embolisation after detorsion. The conservative surgical management of OT should be encouraged to ensure the preservation of ovarian function.In any suspicion for OT, diagnostic laparoscopy should be indicated to preserve ovarian function and future fertility.

Limitations of the study: The low number of patients and retrospective study design were among the limitations of our study.

CONCLUSION

It is concluded that OT is more common in the cases with PCOS. The risk of OT is reduced by decreasing gonadotropin dosage as well as retrieved number of oocyte. Also,prefering frozen-thawed embryo transfer can decrease OT risk in PCOS patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ethical Committee of Beykoz University (Date: 21/12/2020, Decision No: 2020/4).

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. Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility: 7th ed.Philedelphia.Lippincott Williams & Wilkins, 2005.
2. Raouf N, Hikmat R, Munib A, Shamdeen M, Salahaldeen R, Abdullah H. Success of controlled ovarian hyperstimulation and intrauterine insemination in couple with unexplained infertility. J Womens Health Dev 2020; 3: 77-9.
3. Firouz M, Noori N, Ghasemi M, Dashipour A, Keikha N. Comparing the effectiveness of doing intra-uterine insemination 36 and 42 hours after human chorionic gonadotropin (HCG) injection on pregnancy rate: a randomized clinical trial. J Family Reprod Health 2020; 14: 173-9.
4. Hibbard LT. Adnexal torsion. Am J Obstet Gynecol 1985; 152: 456–61.
5. Bekci T, Polat AV, Aslan K, Tomak L, Bilgici MC, Danaci M. Diagnostic performance of diffusion-weighted MRI in the diagnosis of ovarian torsion: comparison of torsed and nonaffected ovaries. Clin imaging 2016; 40: 1029-33.
6. Albayram F, Hamper UM. Ovarian and adnexal torsion: spectrum of sonographic findings with pathologic correlation. J Ultrasound Med 2001; 20: 1083-9.
7. Wilkinson C, Sanderson A. Adnexal torsion-a multimodality imaging review. Clin Radiol 2012; 67: 476-83.
8. Chang HC, Bhatt S, Dogra VS.Pearls and pitfalls in diagnosis of ovarian torsion. Radiographics 2008; 28: 1355-68.
9. Sasaki KJ, Miller CE. Adnexal torsion: review of the literature. J Minim Invasive Gynecol 2014; 21: 196-202.
10. Tanrikulu Y, Tanrıkulu CS, Sabuncuoglu MZ, Kokturk F, Temi V, Bicakci E. Is the neutrophil-to-lymphocyte ratio a potential diagnostic marker for peptic ulcer perforation? A retrospective cohort study. Am J Emerg Med 2016; 34: 403-6.
11. Cass DL. Ovarian torsion. Semin Pediatr Surg 2005; 14: 86-92.
12. Krishnan S, Kaur H, Bali J, Rao K. Ovarian torsion in infertility management-Missing the diagnosis means losing the ovary: ahigh price to pay. J Hum Reprod Sci 2011; 4: 39-42.
13. Shadinger L, Andreotti RF, Kurian RL. Preoperative sonographic and clinical characteristics as predictors of ovarian torsion. J Ultrasound Med 2008; 27: 7-13.
14. Sahlu Z, Negash S, Yusuf L. Adnexal torsion a five-years retrospective review in two hospitals. Ethiop Med J 2014; 52: 155-64
15. Mazouni C, Bretelle F, Menard J, Blanc B, Gamerre M. Diagnosis of adnexal torsion and predictive factors of adnexal necrosis. Gynecol Obstet Fertil 2005; 33: 102-6.
16. Eric J, Balcı O. Diagnostic value of neutrophil to lymphocyte ratio in over torsion. Bozok Tıp Der 2018; 8: 127-33.
17. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: Review. Expert Rev Cardiovasc Ther 2013; 11: 55-9.
18. Tanrikulu CS, Tanrikulu Y, Sabuncuoglu MZ, Karamercan MA, Akkapulu N, Coskun F. Mean platelet volume and red cell distribution width as a diagnostic marker in acute appendicitis. Iran Red Crescent Med J 2014; 16: 10211.
19. Yilmaz H, Celik H, Namuslu M, et al. Benefits of the neutrophil-to-lymphocyte ratio for the prediction of gestational diabetes mellitus in pregnant women. Exp Clin Endocrinol Diabetes 2014; 122: 39-43.
20. Guzel AI, Kokanali MK, Erkilinc S, et al. Predictive role of the neutrophil lymphocyte ratio for invasion with gestational trophoblastic disease. Asian Pac J Cancer Prev 2014; 15: 4203-6.
21. Soysal S, Baki RB. Diagnostic value of neutrophil to lymphocyte ratio in differentiation of ruptured ovarian cysts and adnexal torsion. Turk J Obstet Gynecol 2018; 15: 91-4.
22. Hyttel TE, Bak GS, Larsen SB, Lokkegaard EC: Re-torsion of the ovaries. Acta Obstet Gynecol Scand 2015; 94: 236–44.
23. Weitzman VN, DiLuigi AJ, Maier DB, Nulsen JC. Prevention of recurrent adnexal torsion. Fertil Steril 2008; 90: 2018.
24. Roest J, Mous HV, Zeilmaker GH, Verhoeff A. The incidence of major clinical complications in a Dutch transport IVF programme. Hum Reprod Update 1996; 2: 345–53.
25. Govaerts I, Devreker F, Delbaere A, Revelard P, Englert Y. Short-term medical complications of 1500 oocyte retrievals for in vitro fertilization and embryo transfer. Eur J Obstet Gynecol Reprod Biol 1998; 77: 239–43.
26. Gorkemli H, Camus M, Clasen K.Adnexal torsion after gonadotrophin ovulation induction for IVF or ICSI and its conservative treatment. Arch Gynecol Obstet 2002; 267: 4–6.
27. Tay J, Parker H, Dhange P, Paton-Forrester C, Atiomo W. Isolated torsion of the fallopian tube in a patient with polycystic ovarian syndrome (PCOS). Eur J Obstet Gynecol Reprod Biol 2010; 150: 218–9.
28. Matsuoka S, Kobayashi T, Kusunoki S, Ogishima D. Polycystic ovary syndrome with asynchronous bilateral adnexal torsion in a natural cycle. BMJ Case Rep 2017: bcr-2016218880.
29. Ben-Rafael Z, Bider D, Mashiach S. Laparoscopic unwinding of twisted ischemic hemorrhagic adnexa after in vitro fertilization. Fertil Steril 1990; 53: 569–71.
30. Kemmann E, Ghazi DM, Corsan GH. Adnexal torsion in menotropin-induced pregnancies. Obstet Gynecol 1990; 76: 403–6.
31. Mashiach S, Bider D, Moran O, Goldenberg M, Ben-Rafael Z. Adnexal torsion of hyperstimulated ovaries in pregnancies after gonadotropin therapy. Fertil Steril 1990; 53: 76–80.
32. Berkkanoglu M, Coetzee K, Bulut H, Ozgur K. Risk of ovarian torsion is reduced in GnRH agonist triggered freeze-all cycles: a retrospective cohort study. J Obstet Gynaecol 2019; 39: 212-17.

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Comparison of the ability of the shock index, modified shock index and age shock index to predict mortality in geriatric patients with COVID-19 pneumonia

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ABSTRACT

Introduction: A prognostic measure is urgently needed to predict the severity and mortality of the disease at an early stage in elderly patients with COVID-19 pneumonia. We aimed determine the shock, modified shock and age shock indexes in the early prediction of mortality in advanced-age patients with COVID 19 pneumonia.

Material and Method: The study included patients over 65 years of age with COVID-19 pneumonia confirmed with a positive RT-PCR test. All three indexes were calculated for all the included patients. The ROC analysis was used to determine the predictive values of the indexes in determining mortality.

Results: After evaluating the inclusion and exclusion criteria, the study was completed with a total of 134 patients. It was found that the shock index and age shock index did not statistically significantly differ in predicting mortality (p=0.23 and p=0.06, respectively). In the ROC analysis of the modified shock index in predicting mortality, the area under the curve was 0.658 (95% CI 0.572-0.738) and the Youden index was 0.35 (p=0.02). Cases with higher modified shock index values were found to be 86 times more likely to result in mortality than those with lower values.

Conclusion: The modified shock index is a fast, simple and effective method that can be used to predict mortality during triage in the emergency department in patients aged over 65 with COVID-19 pneumonia confirmed by RT-PCR and tomography.

Keywords: Age shock index, Coronavirus, COVID-19, modified shock index, pneumonia, shock index

INTRODUCTION

The COVID-19 pandemic, which started in December 2019 and still continues its effect across the world, remaining a serious global health problem. Advanced age alone is a risk factor for mortality in patients with COVID-19 pneumonia in elderly patients, COVID-19 pneumonia can quickly lead to acute respiratory distress syndrome and other serious complications (1). Acute respiratory distress syndrome (ARDS) that is unresponsive to treatment can lead to multi-organ failure and death. Therefore, early diagnosis and timely treatment are vital in critically ill patients. In this sense, a prognostic measure is urgently needed to predict the severity and mortality of the disease at an early stage in elderly patients with COVID-19 pneumonia. A simple, inexpensive, fast predictive method that can be evaluated especially at the time of initial presentation to hospital can contribute to reducing mortality. Thus, the clinician can take more aggressive approaches while evaluating treatment protocols and prevent mortality.

The shock index (SI) is a rate that can be easily calculated based on blood pressure and pulse measurements. It basically consists of heart rate/systolic blood pressure value (2). Although it was first used to determine the degree of hypovolemia in cases of hemorrhagic and septic shock, today it is also used as an assessment scale in all types of systemic conditions in which tissue perfusion is impaired (3-6). SI has been found to have a particularly strong association with the left ventricular stroke volume and cardiac output (2). SI has also been reported as an independent risk factor of six-week mortality related to community-acquired pneumonia (7).

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The modified shock index (MSI) is found by dividing the pulse by the mean arterial pressure, and the age shock index (ASI) is obtained by multiplying age and SI. These two derivations were produced considering the theoretical contribution of diastolic blood pressure and age to SI; however, MSI has been suggested to be a better marker than SI in some studies conducted in the emergency department (ED) (8,9). In patients with sepsis, a strong relationship has been observed between myocardial dysfunction and mortality (10). This situation is expected and can be explained by the mean arterial pressure having proven itself as a better marker than systolic or diastolic blood pressure value in terms of organ perfusion while evaluating fluid resuscitation and vasopressor requirement in critically ill patients (11,12).

We did not find any published studies concerning the predictive ability of SI, MSI and ASI for mortality in geriatric patients with COVID-19 pneumonia. Therefore, in the current study

our primary aim was to compare the ability of these three indexes to predict mortality in the geriatric patient population with COVID-19 infection. We considered that taking advantage of these indexes, which can be easily measured at the bedside without any wait, can contribute to treatment strategies and mortality prevention in this disease presenting with high mortality at advanced ages. Our secondary aim was to evaluate the superiority of these indexes over each other and explore the relationship of blood test results, vital signs and comorbidities at the time of presentation with mortality.

MATERIALS AND METHODS

This study was approved by Haydarpaşa Numune Education and Research Hospital Clinical Researches Ethics Committee (Date: 01.03.2021, Decision No: 2021/KK/78). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was planned retrospectively and observationally. Patients who presented to ED due to COVID 19 pneumonia and hospitalized between March 15, 2020 and February 1, 2021 were included in the study. The institutional review board approved the analysis and issued a waiver of consent.

All patients over the age of 65 who were admitted to the ED with COVID-19 complaints, who had oropharyngeal/nasopharyngeal swabs, and who hospitalized between March 1, 2020 and February 1, 2021 were included in the study. Patients whose reverse transcriptase polymerase chainr eaction (RT-PCR) test results were negative and whose ASI, SI and MSI could not be calculated were excluded from the study.

Data were collected from electronic medical hospital records. Data collected included age, sex, vital signs [body temperature, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), mean arterial pressure (MAP), blood oxygen saturation (spO2), body temperature (Temp)] and ASI-SI-MSI. ASI defined as age multiplied by SI. SI was calculated as the ratio of HR to SBP (SI=HR/SBP). MAP was calculated as follows: MAP=[SBP+(2×DBP)]/3. The MSI was calculated as the ratio HR to MAP (MSI= HR/MAP). The formulas were calculated using the vital findings at the time of first admission to the ED.

The primary outcome was in-hospital mortality. The secondary outcome was the superiority of the these indexes to each other and their relationship with comorbidities and blood test results.

Statistical analyses were performed using SPSS v. 19.0 for Windows and Med Calc software packages. Descriptive criteria were presented as mean and standard deviation, median and minimum-maximum values, and percentage distribution. The compliance of the data with normal distribution was checked using the Kolmogorov-Smirnov test. The receiver operating characteristic (ROC) analysis was used to determine the predictive values of the three indexes in mortality. The method described by Delong et al. was used to compare the ROC curves of the indexes. $p < 0.05$ was taken as the level of significance.

RESULTS

After performed the inclusion and exclusion criteria, the study was completed with 134 patients. The demographic data, vital signs, blood test results and index values of the patients are summarized in Table 1. The patients that were survivors (survivors group) and those that died (non-survivors group) were compared in relation to various data. As a result of the statistical analysis, the mean age, body temperature, pulse, neutrophil count, D-dimer, ferritin, SI, MSI and ASI were statistically significantly higher in the non-survivors group than in the survivors group, and the mean saturation and lymphocyte levels of the former were statistically significantly lower compared to the latter (**Table 1**).

The groups were compared with the chi-square test in terms of comorbidity distributions. As a result of the analysis, no statistically significant difference was found between the groups in comorbidity distributions (**Table 2**). In the ROC analysis for mortality prediction, the area under the curve (AUC) was 0.581 [95% confidence interval (CI): 0.493-0.666) and the Youden index was 0.23 for SI. In the same analysis for ASI, AUC was calculated as 0.623 (95% CI: 0.535-0.705) and the

Youden index as 0.26. Accordingly, SI and ASI did not have statistically significant value in predicting mortality (p=0.23 and p=0.06, respectively). In contrast, the ROC analysis for MSI in the prediction of mortality showed that the AUC value was 0.658 (95% CI: 0.572-0.738) and the Youden index was 0.35 (**Figure 1**). Thus, MSI was a statistically significant parameter in mortality prediction (p=0.02). When the cut-off value of MSI in determining mortality was taken as 1.07, it had 55.6% sensitivity, 79.4% specificity, 38.9 positive predictive value, and 86.7 negative predictive value (**Table 3**).

Table 2. Comparison of comorbidities between the discharged and mortality groups

	Survivors n (%)	Non-survivors n (%)	p value*
Diabetes mellitus	51 (47.7)	12 (44.4)	.77
Hypertension	82 (76.6)	19 (70.4)	.50
Coronary artery disease	22 (20.6)	3 (11.1)	.26
Asthma	5 (4.7)	3 (11.1)	.21
COPD	22 (20.6)	4 (14.8)	.50
Chronic heart failure	8 (7.5)	3 (11.1)	.54
Chronic kidney failure	12 (11.2)	5 (18.5)	.31
Other	25 (23.4)	11 (40.7)	.07

*Chi-square test, COPD: Chronic obstructive pulmonary disease

Table 1. Demographic characteristics, clinical and shock index results of the discharged and mortality groups

	Total Mean ± SD Median(min-max) n (%)	Survivors Mean ± SD Median (min-max) n (%)	Non-survivors Mean ± SD Median (min-max) n (%)	p value
Age,years	75.1 (7.4) 74 (65–97)	74.2 (7.1) 73 (65-97)	78.3 (7.7) 77 (67-97)	.01[a]
Gender Male Female		58 (76.3) 49 (84.5)	18 (23.7) 9 (15.5)	.24[b]
Body Temperature, °C	37.0 (0.9) 36.7 (35–40.5)	36.6 (3.3) 36.6 (35.0-39.5)	37.4 (1.2) 36.8 (36.0-40.5)	.03[a]
Pulse, beat/min	84.9 (16.7) 84 (54–120)	84.5 (13.5) 82.5 (54-120)	92.5 (15.5) 90 (60-120)	.006[a]
Systolic blood pressure, mmHg	128.9 (20.2) 130 (80–170)	129.1 (22.3) 130.0 (80– 170)	124.7 (23.5) 126.0 (80-168)	.29[a]
Diastolic blood pressure, mmHg	73.6 (14.2) 70 (40 -114)	74.1 (14.1) 70.0 (49-114)	71.5 (14.9) 70.0 (40-100)	.72[a]
Saturation O_2	93.8 (4.6) 95.5 (77-100)	97.8 (3.7) 96.0 (80-100)	89.9 (5.8) 90.0 (77-98)	.001[a]
Leukocyte count	8.7 (4.8) 8.4 (0.5–29.0)	8.3 (4.5) 7.1 (1.6-29.0)	10.2 (5.5) 9.4 (0.5-21.3)	.08[a]
Neutrophil count	5.9 (4.5) 5.2 (0.01–24.6)	6.2 (4.3) 5.1 (1.0-24.6)	8.5 (5.0) 8.1 (0.01-19.9)	.02[a]
Lymphocyte count	1.5 (0.9) 1.3 (0.2–6.3)	1.5 (0.8) 1.3 (0.2-4.8)	1.3 (1.5) 0.9 (0.2-6.3)	.01[a]
Hemoglobin	11.9 (2.5) 12.3 (1.1–17.1)	12.0 (2.7) 12.3 (1.1-17.1)	11.5 (2.0) 11.9 (6.3-14.5)	.11[a]
Platelet*1000	215.7 (82.9) 196.5 (44–628)	222.9 (84.8) 201.0 (81-628)	187.3 (69.4) 181 (44-337)	.05[a]
D-dimer	1694.0 (1840.4) 1040.0 (140–9989)	1406.9 (1380.9) 940.0 (140-7965)	2832.1 (2807.2) 1480.0 (240-9989)	.004[a]
Ferritin	426.7 (734.8) 201.5 (9–5842)	394.5 (762.1) 186.0 (18-5842)	539.2 (614.1) 360.0 (9-3173)	.004[a]
Mean arterial pressure	87.0 (5.9) 87.3 (67.7–100.7)	87.9 (5.2) 87.7 (76.0 -100.1)	83.7 (7.3) 84.7 (64.7-98.0)	.194[a]
Shock index	0.73 (0.7) 0.67 (0.1–8.0)	0.73 (0.72) 0.66 (0.1-8.0)	0.74 (0.27) 0.73 (0.13-1.46)	.01[a]
Modified shock index	0.97 (0.21) 0.98 (0.15–1.73)	0.96 (0.17) 0.97 (0.17-1.29)	1.07 (0.31) 1.08 (0.15-1.73)	.01[a]
Age shock index	54.3 (46.9) 49.2 (8.2–124.4)	48.6 (10.9) 48.7 (8.2-79.2)	57.9 (22.6) 52.5 (10.8-124.4)	.04[a]

[a]Mann-Whitney U test, [b]Chi-square test
SD, standard deviation

Table 3. ROC analysis results of the modified shock index in predicting mortality

Cut-off value	AUC (95% CI)	Youden index	P value	Sensitivity	Specificity	PPV	NPV
>1.07	0.658 (0.572-0.738)	0.35	.02	55.6%	79.4%	38.9	86.7

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

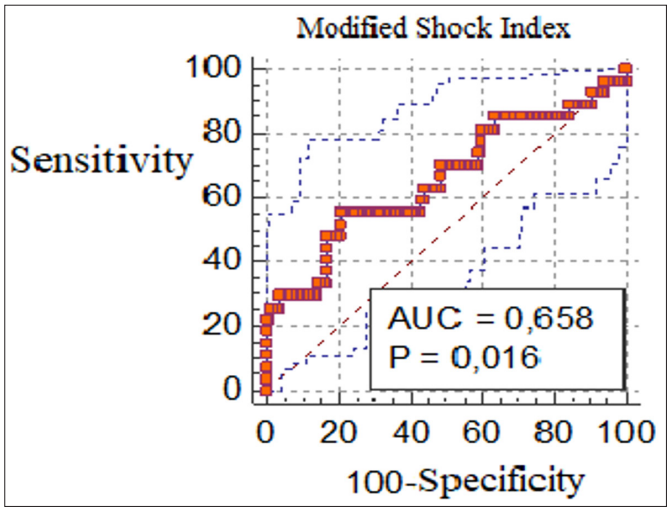

Figure. Receiver operating characteristic curve of the modified shock index

The effect of MSI on the mortality of the patients was examined using the logistic regression analysis after correcting the data according to patient age and body temperature levels which were included in the multivariate model after being determined as significant in the univariate analysis (**Table 4**). The statistical analysis showed that the cases with higher MSI values were 86 times more likely to result in mortality than those with lower MSI values.

DISCUSSION

This is the first study in the literature to compare SI, MSI and ASI in terms of their ability to predict mortality in geriatric patients with COVID-19 pneumonia. In addition to the efficacy of these indexes in mortality prediction, we also aimed to determine their superiority over each other, if any. According to our results, MSI was a simple, fast and effective predictor of mortality in advanced-age patients with COVID-19 pneumonia and it was superior to SI and ASI in this respect.

The main target in the pathogenesis of COVID-19 infection is the respiratory system with severe pneumonia (13). Severe pneumonia caused by human coronaviruses results in acute lung damage and ARDS by triggering a cytokine storm as a result of the uncontrolled excess production of cytokines 14. Increased cytokine release causes dysfunction in all tissues and organs due to the pressure created by inflammation. Vital parameters are almost always the easiest available tools to assess systemic response. Any trauma, infection, tissue and organ disorder that creates stress in the body are objectively reflected by vital parameters in the fastest way. Thus, SI, ASI, and MSI have been derived from these parameters to allow the clinician to predict the severity of the disease. Some studies have determined that SI can be used in many systemic conditions, including sepsis, trauma, pulmonary embolism, and pneumonia (7, 15-17).

In studies evaluating all age groups, it has been reported that advanced age is a single risk factor in COVID-19 pneumonia (18). In our study, when age was evaluated alone, a statistically significant difference was found between the non-survivors and survivor groups. In this sense, while ASI is expected to be an effective parameter, it did not show any statistically significant difference between the non-survivors and survivors' groups in the ROC analysis. This unexpected result can be explained by COVID-19 leading to the development of myocarditis, which is an inflammatory disease of the heart presenting with myocardial damage without an ischemic cause (19).

It has been shown that ACE2 expression, which is the main target cell in COVID-19, is particularly high in the lung, heart, ileum, kidney, and bladder (20). While no decrease in ventricular functions is generally observed in cardiac damage due to COVID-19, patients have uncomplicated lymphocytic myocarditis accompanied by normal cardiac functions (21). In more severe cases, patients may present with jugular venous fullness, peripheral edema, and right upper quadrant pain accompanied by signs of right heart failure (21). The right ventricle is considered to have high compliance and low-resistance pulmonary circulation and is suited to adapt to changes in volume rather than pressure (22).

Since the time it was introduced, SI has been used as a more significant parameter in cases of hemorrhagic shock; i.e., presence of a rapid volume change (3). Systemic infection and myocarditis due to COVID-19 more often cause right ventricular hypertrophy and acute insufficiency symptoms, which have higher adaptability to volume changes (23). In this regard, while the systolic pressure and pulse values of patients may be affected later, this pathophysiological point of view supports the results of our study.

Table 4. Logistic regression analysis of the effect of MSI on mortality

	B	SE	Wald	SD	P	Exp (B)	95% CI Lower	95% CI Upper
Age	0.09	0.034	6.70	1	0.01	1.09	1.02	1.17
Body temperature	0.683	0.249	7.52	1	0.006	1.98	1.21	3.22
MSI	4.46	1.52	8.57	1	0.003	86.146	4.36	1701.6
Constant	-37.9	10.53	12.98	1	0	0		
Nagelkerke R2=0.283 Omnibus chi-square=25.89 p=0.001 Hosmer and Lemeshov=0.16								

MSI, modified shock index; SE, standard error; SD, standard deviation; CI, confidence interval

When calculating MSI, the pulse value is divided by the mean arterial pressure. The mean arterial pressure is a stronger value than other vital parameters and used to evaluate the contraction force of the heart and vasopressor requirement of patients. In our study, a striking finding was that the cases with higher MSI were 86 times more likely to result in mortality than those with lower MSI values.

In our study, the number of patients was limited due to the selection criteria including RT-PCR positivity and a specific age group being examined. This limitation can be avoided by conducting further studies in multiple centers with a prospective and long-term design.

According to the ROC analysis conducted in the current study, SI and ASI were not effective parameters in the prediction of mortality in geriatric patients with COVID-19 pneumonia. Although these two indexes were previously reported to be effective methods in the evaluation of sepsis and other pneumonia cases, our results did not show similar efficacy in COVID-19 pneumonia (24).

CONCLUSION

MSI is a fast, simple and effective method that can be used to predict mortality during triage in the ED in geriatric patients with COVID-19 pneumonia confirmed by RT-PCR.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Haydarpaşa Numune Education and Research Hospital Clinical Researches Ethics Committee (Date: 01.03.2021, Decision No: 2021/KK/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.

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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. Rohat A, Erdem K, Bahadirli S. Thecomparison of two risk prediction models specific for COVID-19: The Brescia-COVID Respiratory Severity Scale versus the Quick COVID-19 Severity Index. Disaster Med Public Health Prep 2021: 1-17.
2. Rady MY, Smithline HA, Blake H, Nowak R, Rivers E. A comparison of the shock index and conventional vital signs to identify acute, criticalillness in theemergency department. Ann Emerg Med 1994; 24: 685-90.
3. Allgöwer M, Burri C. "Schockindex". Dtsch Med Wochenschr 1967; 92: 1947-50.
4. Althunayyan SM, Alsofayan YM, Khan AA. Shock index and modified shock index as triage screening tools for sepsis. J Infect Public Health 2019; 12: 822-6.
5. Pandit V, Rhee P, Hashmi A, et al. Shock index predicts mortality in geriatric trauma patients: an analysis of the National Trauma Data Bank. J. Trauma Acute Care Surg 2014; 76: 1111-5.
6. McCall SJ, Musgrave SD, Potter JF, et al. The shock index predicts acute mortality outcomes in stroke. Int J Cardiol 2015; 182: 523-7.
7. Sankaran P, Kamath AV, Tariq SM, et al. Are shock index and adjusted shock index useful in predicting mortality and length of stay in community-acquired pneumonia? Eur J Intern Med 2011; 22: 282-5.
8. Liu YC, Liu JH, Fang ZA, et al. Modified shock index and mortality rate of emergency patients. World J Emerg Med 2012; 3: 114.
9. Zarzaur BL, Croce MA, Fischer PE, Magnotti LJ, Fabian TC. New vitals after injury: shock index for the young and age shock index for the old. J Surg Res 2008; 147: 229-36.
10. Jayaprakash N, Gajic O, Frank RD, Smischney N. Elevated modified shock index in early sepsis is associated with myocardial dysfunction and mortality. J Crit Care 2018; 43: 30-5.
11. Levy MM, Rhodes A, Evans LE, et al. COUNTERPOINT: should the Surviving Sepsis Campaign guidelines be retired? No. Chest 2019; 155: 14-7.
12. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004; 32: 1637-42.
13. 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.
14. Sun X, Wang T, Cai D, et al. Cytokine storm İntervention in the early stages of COVID-19 pneumonia. Cytokine Growth Factor Rev 2020; 53: 38-42.
15. Cannon CM, Braxton CC, Kling-Smith M, et al. Utility of the shock index in predicting mortality in traumatically injured patients. J. Trauma Acute Care Surg 2009; 67: 1426-30.
16. Otero R, Trujillo-Santos J, Cayuela A, et al. Haemodynamically unstable pulmonary embolism in the RIETE Registry: systolic blood pressure or shock index? Eur Respir J 2007; 30: 1111-6.
17. Rousseaux J, Grandbastien B, Dorkenoo A, Lampin ME, Leteurtre S, Leclerc F. Prognostic value of shock index in children with septic shock. Pediatr Emerg Care 2013; 29: 1055-9.
18. Du RH, Liang LR, Yang C-Q, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020; 55-5.
19. Esfandiarei M, McManus BM. Molecular biology and pathogenesis of viral myocarditis. AnnuRev Pathol Mech Dis 2008; 3: 127-55.
20. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020: 1-8.
21. Hu H, Ma F, Wei X, Fang Y. Corona virüs fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J 2021; 42: 206.
22. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardio vascular disease, part I: anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation 2008; 117: 1436-48.
23. Martínez-Mateo V, Fernández-Anguita MJ, Paule A. Electro cardiographic signs of acute right ventricular hypertrophy in patientswith COVID-19 pneumonia: A clinica lcases eries. J. Electrocardiol 2020; 62: 100-2.
24. Yasaka Y, Khemani RG, Markovitz BP. Is shock index associated with outcome in children with sepsis/septicshock? Pediatr Crit Care Med 2013; 14: e372-e9.

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Evaluation of the relationship between disease activity and serum bilirubin, albumin, and uric acid levels in Crohn's disease

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ABSTRACT

Objective: Oxidative stress and antioxidant deficiency play key roles in the pathogenesis of gastrointestinal damage associated with Crohn's disease (CD). Serum bilirubin, uric acid (UA) and albumin are non-enzymatic antioxidants that play a role in oxidative stress control. In this study, it was aimed to evaluate the change in serum bilirubin, UA and albumin levels due to disease activity.

Material and Method: This study was designed as a single-center, cross-sectional and retrospective. The clinical and demographic data of the patients, disease activity, as well as serum albumin, UA, and bilirubin values were recorded from the hospital database. Study variables were statistically analyzed between patient and control groups based on disease activity.

Results: A total of 234 people, 114 with CD and 120 with controls, were included in the study. Total bilirubin, direct bilirubin and albumin levels were found to be significantly lower in the CD than in the health control ($p=0.045$, $p<0.001$, $p<0.001$). There was a significant difference in total bilirubin, direct bilirubin, indirect bilirubin and albumin levels between the control group and active CD ($p=0.009$; $p=0.001$; $p=0.037$; $p<0.001$); no significant difference with the UA level ($p=0.992$). There was a significant difference in direct bilirubin levels between the control group and remission CD ($p=0.005$); no difference in total bilirubin, indirect bilirubin, albumin, and UA levels ($p=0.263$; $p=0.440$; $p=0.112$; $p=0.365$, respectively).

Conclusion: Antioxidant capacity reaches levels similar to the healthy population in patients who achieve remission with medical treatment.

Keywords: Albumin, bilirubin, Crohn's disease, oxidative stress, uric acid

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease that can affect the gastrointestinal tract from mouth to rectum (1). Its annual incidence varies according to geographical region, environmental factors, genetic predisposition and lifestyle (2). With the increasing incidence of inflammatory bowel disease, the diagnosis and treatment of CD has gained importance in terms of gastroenterology (3). Since the etiology of the disease has not been fully elucidated, the goal of treatment is to convert the disease from active to remission. Multiple laboratory indices are used to diagnose and evaluate the activity of CD. Some laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), red cell distribution width (RDW), tumor necrosis factor, and fecal calprotectin were found to be associated with the activity of the disease (4). Such laboratory tests not only show the activity of the disease, but may also be indicative of existing bacterial infection. Therefore, there is a need for low-cost and non-invasive tests that can evaluate the activity of the disease, with high patient compliance.

Bilirubin, the end product of heme metabolism, is a potent endogenous antioxidant (5). While bilirubin was previously considered as a cytotoxic waste with potential toxicity, it has recently come to the fore with its strong antioxidant, anti-inflammatory and immunosuppressive properties (5). The antioxidant property of bilirubin has been demonstrated in patients with systemic lupus erythematosus (6) and polymyositis (7). Uric acid (UA) is the end product of purine catabolism and has been shown to scavenge more than half of the free radicals in

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the blood as an antioxidant (8). The antioxidant role of UA was demonstrated in a study conducted with patients with myasthenia gravis (9). Serum albumin is known as an antioxidant against oxidative damage.

Considering the role of serum bilirubin, UA and albumin in inflammatory diseases, we aimed to investigate the relationship between these values and the activity of CD.

MATERIAL AND METHOD

The study was approved by Gazi University Faculty of Medicine, Clinical Research Ethics Committee (Date: 7/12/2020, Decision No: 834). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

This study is a single-center retrospective cohort study, and patients with CD who applied to the gastroenterology outpatient clinic between 1 October 2015 and 1 October 2020 were included. When the sample was calculated with 95% confidence interval and 80% power of analysis, the sample size was calculated as 87 people. Our study included patients aged 18 years and older, who were diagnosed with Crohn's disease based on medical history, clinical features, endoscopic, histopathological, imaging methods and laboratory tests, and whose follow-up and medical treatment continued. The healthy control group was selected from the patients who applied to the general internal medicine outpatient clinic in the same period.

Determination of Study Variables and Disease Activity

In the anamnesis form obtained from the hospital database of the patients diagnosed with Crohn's disease; gender, age, date of diagnosis, localization of the disease, presence of systemic disease, extraintestinal findings, documentation of current and past medical treatment were recorded. Serum total bilirubin, direct bilirubin, indirect bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, UA, CRP, ESR, RDW, globulin, hemoglobin, hematocrit, white blood cell, lymphocyte, neutrophil, monocytes, ferritin, mean platelet volume (MPV) values were examined. Disease activity was determined at the time of admission to the hospital using the information in the anamnesis form obtained from the database, clinical features and laboratory parameters, and the CD activity index (CDAI) score. Patients with a CDAI score below 150 were considered in remission, 150-220: mild-moderate, 221-450: moderate-severe, >450: severe fulminant Crohn's disease. Age at diagnosis, site of involvement, type of disease and presence of perianal disease were determined according to the Montreal classification.

Statistical Analysis

Statistical analyzes were performed using the SPSS for Windows Version 22. Frequencies were stated for the variables in the categorized data (qualitative), and for the numerical data (quantitative) variables, the means ± standard deviation if appropriate for the normal distribution, and the median (min-max) values if not for the normal distribution. Whether the variables fit the normal distribution or not was evaluated with the Kolmogorov Smirnov test. Parametric tests (Independent Sample t Test) were used for the variables showing normal distribution, and nonparametric tests (Chi-Square, Mann Withney U Test) were used for those that did not. Kruskal Wallis Test was used for comparison of triple numeric data. Spearman correlation test was used for the correlation between continuous variables. The statistical significance of this study was accepted as $p \leq 0.05$.

RESULTS

A total of 234 people, 114 with CD and 120 with controls, were included in the study. 49% (n=56) of CD and 39% (n=47) of the healthy control group were male. There was no statistically significant difference between the two groups by gender (p=0.125). There was no statistically significant difference in the mean age of the CD (39.36± 12.26) and control group (39.12±13.63)(p=0.886). While 28.9% (n=33) of CD were in the active period, 71.1% (n=81) were in remission, and the clinical demographic characteristics of the entire group are summarized in **Table 1**.

There was a statistically significant difference in total bilirubin, direct bilirubin, albumin, globulin, ALP, ferritin, hemoglobin, neutrophil, lymphocyte, platelet, RDW and MPV values between the CD and control group ($p<0.05$) (**Table 2**). There was no statistically significant difference between indirect bilirubin, UA, AST, ALT, GGT, leukocytes, monocytes, and hematocrit values ($p>0.05$) (**Table 2**).

A statistically significant difference was found between CRP and albumin levels between remission and active CD ($p<0.001$, $p<0.001$). No statistically significant difference was found between gender, age, total bilirubin, direct bilirubin, indirect bilirubin and UA levels (p=0.361, p=0.476, p=0.170, p=0.280, p=0.233, p=0.478, respectively) (**Table 3**) .

There was a statistically significant difference between the control group and active CD, levels of total bilirubin, direct bilirubin, indirect bilirubin, and albumin (p=0.009, p=0.001, p=0.037, $p<0.001$, respectively). There was no statistically significant difference between the UA level (p=0.992) (**Table 4**). There was a statistically significant difference between direct bilirubin levels

between control and remission CD (p=0.005). No statistically significant difference was found between total bilirubin, indirect bilirubin, albumin, and UA levels (p>0.05) (**Table 4**).

There was a statistically significant difference in terms of disease activity severity (mild, moderate and severe), albumin and CRP (p<0.001, p<0.001, respectively). There was no statistically significant difference between total bilirubin, direct bilirubin, indirect bilirubin and UA levels (p=0.300, p=0.378, p=0.340, p=0.173, respectively).

When the laboratory parameters of CD patients who received only azathioprine treatment and those who received other treatment types were compared, no statistically significant difference was found between total bilirubin, direct bilirubin, indirect bilirubin, albumin, and UA values (p>0.05) (**Table 5**).

No correlation was found between the duration of treatment and serum total bilirubin, direct bilirubin, indirect bilirubin, UA, and albumin values (p=0.845, r=0.019; p=0.728, r=0.033; p=0.997 r=0.000; p=0.894, r=0.013; p=0.965 r=0.004, respectively).

Table 1. Demographic and clinical characteristics of CD

	CD, n=114	
Disease activity	**n**	**%**
Active	33	28.9
Remission	81	71.1
Gender		
Male	56	49
Female	58	51
Comorbidities		
Yes	30	26.4
No	84	73.6
Age at diagnosis		
<16 years (A1)	7	6.1
17-40 years (A2)	78	68.4
>40 years (A3)	29	25.5
Disease localization		
Ileal (L1)	32	29.6
Colonic (L2)	36	33.3
Ileocolonic (L3)	38	35.2
Upper GIS involvement (L4)	2	1.9
Disease Behaviour		
Inflammatory (B1)	62	54.85
Obstructive/stenosing (B2)	19	16.85
Penetrating/fistulizing (B3)	20	17.65
Perianal (P)	12	10.65
Extraintestinal symptom		
Yes	24	20.5
No	90	79.5
Disease activity (CDAI score)		
<150 remission	81	71.1
150-220 mild moderate	23	20.2
220-450 moderate-severe	10	8.8
>450 fulminant	0	0
Type of treatment		
Vedolizumab/Certolizumab	13	11.4
5-ASA	19	16.6
Azathioprine±anti TNF	37	32.4
Prednol or unknown	8	7.0
Azathioprine±5-ASA	37	32.4
Only azathioprine treatment	18	15.7
Other treatments	96	84.2

CD=Crohn's disease,

Table 2. Comparison of demographic characteristics and laboratory parameters in the study group

	CD, n=114	Control, n=120	P
Gender n (%)			0.125
Male	56 (49%)	47 (39%)	
Female	58 (51%)	73 (61%)	
Age (years)*	39.36±12.26	39.12±13.63	0.886
CRP, mg/L**	7.30 (1-206)		
Total bilirubin, mg/dL	0.52 (0.13-2.45)	0.58 (0.26-2.37)	0.045
Direct bilirubin, mg/dL	0.10 (0.03-0.37)	0.13 (0.05-0.51)	<0.001
Indirect bilirubin, mg/dL	0.42 (0.05-2.14)	0.46 (0.11-1.86)	0.128
Albumin, g/dL	4.30 (1.50-8.40)	4.50 (3.60-5.10)	<0.001
UA, mg/dL	4.85 (2.20-8.80)	4.70 (2.20-8.30)	0.481
AST, U/L	19.00 (10-225)	20.00 (11-42)	0.477
ALT, U/L	16.00 (2-271)	17.00 (7-69)	0.486
ALP, U/L	90.00 (47-230)	77.50 (38-164)	0.003
GGT, U/L	22.00 (7-277)	18.00 (8-127)	0.054
Globulin, g/dL	3.15 (2.30-4.70)	2.90 (2.30-3.90)	<0.001
Ferritin, ng/mL	35.00 (2-595)	21.00 (2-175)	0.007
Hemoglobin, g/dL	13.60 (7.40-18.10)	13.95 (10.00-18.30)	0.007
Leukocyte, $\times10^3$/uL	7380.00 (3110-22620)	7100.00 (3790-12720)	0.140
Neutrophil, $\times10^3$/uL	4425.00 (1150-18450)	3960.00 (670-7170)	0.002
Lymphocyte, $\times10^3$/uL	2035.00 (300-4550)	2275.00 (990-4770)	0.002
Monocyte, $\times10^3$/uL	560.00 (120-1610)	560.00 (230-1140)	0.488
Platelet, $\times10^3$/uL	303000.00 (110000-766000)	276500.00 (163000-439000)	0.001
RDW, %	13.65 (12-32)	13.00 (11-19)	<0.001
MPV, fL	9.70(8.10-21.70)	10.20 (8.40-12.90)	0.002
Hematocrit, %	41.50 (22-53)	42.05 (34-54)	0.174
Sedimentation, mm/h	20.50 (2-105)		

* mean ±standard deviation. **median(min-max). CD=Crohn's disease, ALT=alanine aminotransferase. ALP=alkaline phosphatase. AST=aspartate aminotransferase. CRP=C reactive protein. GGT=gammaglutamyl transferase. MPV=mean platelet volume. RDW= red cell distribution width. UA=uric acid

Table 3. Comparison of laboratory parameters according to activity in CD

	Remission CD, n=81	Active CD, n=33	P
Gender n (%)			
Male	42 (51.9)	14 (42.4)	0.361
Female	39 (48.1)	19 (57.6)	
Age (years)*	39.77±12.03	38.36±12.95	0.476
CRP, mg/L**	47.37 (1-73)	78.36 (12-105)	<0.001
Total bilirubin, mg/dL	0.52 (0.13-2.45)	0.50 (0.26-0.83)	0.170
Direct bilirubin, mg/dL	0.11 (0.03-0.37)	0.09 (0.06-0.19)	0.280
Indirect bilirubin, mg/dL	0.42 (0.05-2.14)	0.40 (0.20-0.66)	0.233
Albumin, g/dL	4.40 (1.50-8.40)	4.00 (2.90-7.80)	<0.001
UA, mg/dL	4.95 (2.30-8.80)	4.45 (2.20-7.70)	0.478

*mean ±standard deviation. **median(min-max). CD=Crohn's disease, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRP=C reactive protein, UA=uric acid.

Table 4. Comparison of laboratory parameters of control group and active and remission CD

	Control, n=120	Active CD, n=33	P	Remission CD, n=81	P
Total bilirubin,mg/dL*	0.58 (0.26-2.37)	0.50 (0.26-0.83)	0.009	0.52 (0.13-2.45)	0.263
Direct bilirubin,mg/dL	0.13 (0.05-0.51)	0.09 (0.06-0.19)	0.001	0.11 (0.03-0.37)	0.005
Indirect bilirubin,mg/dL	0.46 (0.11-1.86)	0.40 (0.20-0.66)	0.037	0.42 (0.05-2.14)	0.440
Albumin, g/dL	4.50 (3.60-5.10)	4.00 (2.90-7.80)	<0.001	4.40 (1.50-8.40)	0.112
UA. mg/dL	4.70 (2.20-8.30)	4.45 (2.20-7.70)	0.992	4.95 (2.30-8.80)	0.365

*median(min-max), CD=Crohn's disease, UA=uric acid

Table 5. Comparison of laboratory parameters in CD receiving azathioprine only and other treatments

	Only azathioprine treatment, n=18	Other treatments, n=96	P
Total bilirubin mg/dL*	0.52 (0.23-1.35)	0.52 (0.13-2.45)	0.887
Direct bilirubin mg/dL	0.10 (0.05-0.26)	0.11 (0.03-0.37)	0.832
Indirect bilirubin mg/dL	0.40 (0.09-0.66)	0.42 (0.05-2.14)	0.657
Albumin g/dL	4.30 (3.90-4.80)	4.30 (1.50-8.40)	0.617
UA. mg/dL	4.50 (2.60-6.90)	4.90 (2.20-8.80)	0.317

*median(minimum-maximum), CD=Crohn's disease, UA=uric acid

DISCUSSION

To the best of our knowleged, our study is the first reported from Turkey to examine the relationship between serum bilirubin, albumin and UA which are non-enzimatic antioxidant molecules and disease activity in patients with CD followed up with medical treatment.

In the current study, found that serum total bilirubin and albumin levels, which reflect the change in serum antioxidant capacity due to the increase in inflammation-related oxidative stress, were significantly lower in CD compared to the healthy controls. But there was no significant difference in indirect bilirubin and UA levels.

In the study of Su et al. (10) serum bilirubin, albumin, and UA levels were found to be lower in newly diagnosed Crohn's patients who had not yet received medical treatment compared to the healthy controls, and this was associated with excessive consumption and destruction of serum bilirubin, albumin, and UA.

In a study by Zhu et al. (11) UA levels were found to be higher in inflammatory bowel disease compared to healthy controls, similar to present study, and it was observed that UA level increased with disease activity. UA is a parameter that undergoes renal elimination and is affected by renal functions. UA is a parameter that undergoes renal elimination and is affected by renal functions. Creatinine, on the other hand, is a biochemical parameter that changes depending on muscle mass and dietary protein, and it is a test that is affected by both kidney functions and nutritional status. For these reasons, in the same study, they evaluated the UA level, which is one of the parameters that will show the decrease in the endogenous antioxidant capacity of the patients, as the UA/creatinine ratio in order to minimize the interpretation errors. The lack of significant difference in UA level between the healthy controls and CD in the current study may be related to the medical treatment, the possible effect of medical treatment on the redox balance, or the fact that UA is a parameter affected by the nutritional status. In addition, oxidative stress management in the body is provided by enzymatic and non-enzymatic mechanisms, and the net effect of medical treatment on the enzymatic antioxidant system is unknown.

In the current study, a statistically significant difference was found between albumin and CRP levels and disease activity, but no significant difference was found between

disease activity and total bilirubin, direct bilirubin, indirect bilirubin and UA levels. Kekilli et al. (12) found no difference in serum albumin levels between newly diagnosed active CD and CD patients in remission. The reason for this different result compared to the current study may be due to the low number of patients in remission in this study.

Albumin is a negative acute phase reactant and decreases as disease activity increases, while CRP level increases in line with the severity of inflammation. At the same time, albumin can be affected by the nutritional status of patients.

In the study of Su et al. (10) similar to present study, no significant difference was found between disease activity and UA level. They showed that as the severity of the disease increased, serum bilirubin, albumin and UA levels decreased, and CRP levels increased. The difference of this study from the current study is that newly diagnosed patients who have not yet received medical treatment were included in the study. The lack of a significant difference between disease activity and serum bilirubin and UA levels in the current study may be due to the small number of active patients. The fact that the patients were under medical treatment, and the different effects of the drugs used on the redox balance (10).

In the current study, in the comparison between remission and active Crohn's patients, CRP level was significantly higher and albumin level was significantly lower in patients with active disease. In contrast, no statistically significant difference was found between serum bilirubin and UA levels. The reason for these results is that all patients are receiving medical treatment and the number of active patients is relatively low. Serum bilirubin and albumin levels were found to be significantly lower in active Crohn's disease compared to healthy controls, but there was no statistically significant difference between UA values. If there is no difference between UA levels, it can be considered that all Crohn's patients should be under medical treatment. While there was a significant difference only in direct bilirubin levels between healthy controls and CD in remission, there was no significant difference in serum total bilirubin, indirect bilirubin, albumin, and UA levels.

In the light of this information, it can be concluded that redox balance is established in the body and serum antioxidant capacity reaches levels similar to the healthy population in patients who are in remission with medical treatment.

There is increased oxidative stress and decreased antioxidant capacity in active CD, and serum antioxidant capacity reaches levels similar to the healthy controls in patients with remission (13-15).

In the study of Szczeklik et al. (16) serum bilirubin and albumin levels were found to be significantly lower in active CD compared to healthy controls and inactive CD patients, and present values were negatively correlated with disease severity. Lenicek et al. (17) reported that each 1 mmol/L decrease in serum bilirubin is associated with a 13% increase in the risk of developing CD. Schieffer et al. (18) suggested that the decrease in serum bilirubin is due to inflammation and that this phenomenon is observed not only in CD but also in various inflammatory diseases.

An Australian study (16) suggested that bilirubin levels are significantly lower in severe asthma, while inflammation affects antioxidant vitamins and bilirubin levels in asthmatics. This study shows the relationship between the changing serum concentration of bilirubin and albumin and oxidative imbalance in inflammation, similar to our study. In the study by Yang et al. (9) serum bilirubin, UA, albumin and creatinine levels were found to be lower in patients with myasthenia gravis, an autoimmune disease, when compared to the healthy controls. In the same study, when grouped according to the degree of disease progression, no significant difference was found in serum bilirubin levels, and serum UA, albumin and creatinine levels were negatively correlated with disease progression.

Peng et al. (19) found that serum total bilirubin, indirect bilirubin, UA and albumin levels were significantly lower in patients with neuromyelitis optica compared to healthy controls. Li et al. (20), found significantly lower serum bilirubin, UA and albumin levels in patients with newly was diagnosed pemphigus vulgaris that also known as a autoimmun severe bullous dermatosis compared to healthy controls. Albumin levels when compared to healthy controls.

Since CD is an inflammatory disease, it has been suggested that decreased antioxidant reserve is probably the pathogenic mechanism in the disease. Oxidative stress and antioxidant deficiency are thought to play a key role in the pathogenesis of CD-related gastrointestinal damage (15).

In the current study, did not find a significant difference in serum bilirubin, UA, and albumin levels between patients treated with azathioprine alone and those receiving other treatments. Neubauer et al. (20) investigated the possible relationship between non-enzymatic antioxidants and azathioprine treatment. In this study, no significant difference was found in serum UA levels between patients who received and did not receive azathioprine. Azathioprine may have opposite effects on systemic antioxidants. On the one hand, it causes an increase in systemic hydrogen peroxide, leading to cytotoxicity

mediated by drug-induced oxidative stress in hepatocytes or T lymphocytes. On the other hand, azathioprine, which can undergo biotransformation through three different enzymatic systems and is metabolized by xanthine oxidase, produces thioric acid. Thioric acid is a compound equipped with a free sulfhydryl group, which has antioxidant capacity like UA. It has been shown in studies that sulfur derivatives of UA have neuroprotective effects and reduce ischemic brain damage (21).

Lemarachel et al. (22) measured protein oxidation levels in patients with rheumatoid arthritis who were treated with infliximab, and it was interpreted that redox balance was achieved due to the decrease in serum protein carbonyl groups after infliximab treatment. Monoclonal antibodies (anti-TNF-α) inhibit the production of activated macrophage and other proinflammatory cytokines that increase T cell infiltration. A potent anti-inflammatory effect appears, including lysis of activated immune cells and induction of apoptosis by TNF-α neutralization (23).

Bednarek et al. (24) conducted a study on oxidative stress parameters in patients treated with corticosteroids for infiltrative Graves' ophthalmopathy. They found that oxidative stress parameters decreased during treatment and concluded that corticosteroids can temporarily reduce oxidative load. Corticosteroids are drugs that have anti-inflammatory and immunosuppressive effects by reducing lymphocyte proliferation and inhibiting inflammatory mediators secreted by macrophages. Thus, corticosteroids prevent the production of reactive free radicals. With the reduction of immune cells and mediators, the formation and release of free radicals is reduced, and oxidative stress is prevented.

There are some limitations in the current study. First, this is a retrospective study of patients with CD and has a small sample size. Secondly, due to the small number of patients with active CD, it was prevented to reach clear conclusions in evaluating the relationship between bilirubin, albumin, UA and disease activation. Third, the relationship between some antioxidant enzymes (SOD, GSH-Px, catalase) and disease activity was not evaluated in the present study. Finally, a proportion of patients with CD have been treated with azathioprine, and the impact of this drug on outcomes cannot be excluded.

CONCLUSION

Albumin, bilirubin and UA, which are cost-effective tests that are routinely used in clinical practice, may be useful biomarkers in the detection of antioxidant status in Crohn's disease and may guide the early diagnosis of the disease. Larger-scale studies are needed for the use of these biomarkers for the evaluation of disease activity and treatment response.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Gazi University Faculty of Medicine, Clinical Research Ethics Committee (Date: 7/12/2020, Decision No: 834).

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

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REFERENCES

1. Wilkins T, Jarvis K, Patel J. Diagnosis and management of Crohn's disease. Am Fam Physician 2011; 84: 1365-75.
2. Yang H, Li Y, Wu W, et al. The incidence of inflammatory bowel disease in Northern China: a prospective population-based study. PloS one 2014; 9: e101296.
3. Cosnes J, Gower–Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology 2011; 140: 1785-94.
4. Ananthakrishnan AN, Cheng SC, Cai T, et al. Serum inflammatory markers and risk of colorectal cancer in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2014; 12: 1342-8.
5. Jangi S, Otterbein L, Robson S. The molecular basis for the immunomodulatory activities of unconjugated bilirubin. Int J Biochem Cell Biol 2013; 45: 2843-51.
6. Dos Santos BH, de R Almeida CM, Skare TL. Systemic Lupus Erythematosus activity and serum bilirubins. Acta Reumatol Port 2013; 38: 242-6.
7. Peng Y, Zhang L, Pan G, et al. A potential clinical usefulness of measuring serum bilirubin levels in patients with polymyositis. Eur Rev Med Pharmacol Sci 2016; 20: 631-5.
8. Ames BN, Cathcart R, Schwiers E, et al. Uric acid provides an antioxidant defense in humans against oxidant-and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 1981; 78: 6858-62.
9. Yang D, Su Z, Wu S, et al. Low antioxidant status of serum bilirubin, uric acid, albumin and creatinine in patients with myasthenia gravis. Int J Neurosci 2016; 126: 1120-6.
10. Su Q, Li X, Mo W, et al. Low serum bilirubin, albumin, and uric acid levels in patients with Crohn's disease. Medicine (Baltimore) 2019; 98: e15664.
11. Zhu F, Feng D, Zhang T, et al.Altered uric acid metabolism in isolated colonic Crohn's disease but not ulcerative colitis. J Gastroenterol Hepatol 2019; 34: 154-61.
12. Kekilli M, Tanoğlu A, Karaahmet F et al. Midkine level may be used as a noninvasive biomarker in Crohn's disease. Turk J Med Sci 2020; 50: 324-9.
13. Boehm D, Krzystek-Korpacka M, Neubauer K, et al. Lipid peroxidation markers in Crohn's disease: the associations and diagnostic value. Clin Chem Lab Med 2012; 50: 1359-66.
14. Wendland BE, Aghdassi E, Tam C, et al. Lipid peroxidation and plasma antioxidant micronutrients in Crohn disease. Am J Clin Nutr 2001; 74: 259-64.

15. Koutroubakis IE, Malliaraki N, Dimoulios PD, et al. Decreased total and corrected antioxidant capacity in patients with inflammatory bowel disease. Dig Dis Sci 2004; 49: 1433-7.
16. Szczeklik K, Krzyściak W, Cibor DA, et al. Evaluation of plasma concentrations of selected antioxidant parameters in patients with active Crohn's disease. Folia Medica Cracoviensia 2018; 58: 119-30
17. Leníček M, Ďuricová D, Hradsky O, et al. The Relationship Between Serum Bilirubin and Crohn's Disease. Inflamm Bowel Dis 2014; 20: 481-7.
18. Schieffer KM, Bruffy SM, Rauscher R, et al. Reduced total serum bilirubin levels are associated with ulcerative colitis. PloS one 2017; 12: e0179267.
19. Peng F, Yang Y, Liu J, et al. Low antioxidant status of serum uric acid, bilirubin and albumin in patients with neuromyelitis optica. Eur J Neurol 2012; 19: 277-83.
20. Li WC, Mo LJ, Shi X, et al. Antioxidant status of serum bilirubin, uric acid and albumin in pemphigus vulgaris. Clin Exp Dermatol 2018; 43: 158-63.
21. Neubauer K, Kempinski R, Matusiewicz M, et al. Nonenzymatic Serum Antioxidant Capacity in IBD and Its Association with the Severity of Bowel Inflammation and Corticosteroids Treatment. Medicina (Kaunas) 2019; 55: 88.
22. Lemarechal H, Allanore Y, Chenevier-Gobeaux C, et al. Serum protein oxidation in patients with rheumatoid arthritis and effects of infliximab therapy. Clinica Chimica Acta 2006; 372: 147-53.
23. Pereira C, Grácio D, Teixeira JP, et al. Oxidative stress and DNA damage: implications in inflammatory bowel disease. Inflamm Bowel Dis 2015; 21: 2403-17.
24. Bednarek J, Wysocki H, Sowiński J. Peripheral parameters of oxidative stress in patients with infiltrative Graves' ophthalmopathy treated with corticosteroids. Immunol Lett 2004; 93: 227-32.

Original Article

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Evaluation of colonoscopic findings in patients undergoing colonoscopy due to positive fecal occult blood test: a single center experience

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ABSTRACT

Aim: Fecal occult blood test is used in the early diagnosis of colorectal cancer. We aimed to evaluate the colonoscopic and pathological findings of patients who underwent colonoscopy due to positive fecal occult blood test in a tertiary center.

Material and Method: Patients who had a positive fecal occult blood test and referred to the Health Sciences University, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital endoscopy unit for colonoscopy were included in this study. Age, gender, colonoscopy findings and pathology results of the patients were recorded. Statistical analyzes were performed with SPSS v21.0.

Results: Two hundred and twenty three patients were included in the current study. Of the patients, 101 (45.3%) were male and 122 (54.7%) were female, with a mean age of 53.2 (18-90 years). Endoscopic diagnoses were as 49 (22%) polyp, 13 (5.8%) colon cancer, 4 (1.8%) inflammatory bowel disease, 15 (6.7%) diverticulum, 63 (28.3%) perianal disease, 79 (35.4%) normal colonoscopic findings. Pathological features of colon polyps were as; tubular adenoma in 51%, tubulovillous adenoma in 18.4%, serrated adenoma in 2%, and hyperplastic polyp in 28.6%. Colonoscopic findings of patients according to age groups (over and under 50 years of age); the incidence of polyps (p=0.01) and diverticulum (p=0.001) were significantly higher in patients older than 50 years, while perianal diseases (p=0.031) and normal colonoscopic findings (p=0.008) were higher in patients younger than 50 years of age.

Conclusion: Colon pathology was detected in approximately 2/3 of the patients presenting with a positive fecal occult blood test. This test is an inexpensive, easily applicable method that helps to detect colon cancer and precursor lesions, as well as pathologies such as subclinical inflammatory bowel disease and diverticulum causing chronic blood loss.

Keywords: Fecal occult blood test, colonoscopy, colorectal cancer, polyp

INTRODUCTION

Colorectal cancers are the third most common cancer in the world and one of the leading causes of cancer-related deaths (1). Detection of colorectal cancers at an early stage is the most important part of the survival of the disease, allowing curative endoscopic or surgical treatments. With effective screening programs, it may be possible to detect, treat and even prevent the disease in the early period (2).

In Turkey, colon cancer screening program has been carried out since September 2014 by fecal occult blood test (FOBT) every 2 years and colonoscopy every 10 years in healthy individuals aged 50-70 years (3). In addition to that, FOBT is used in the early diagnosis of colorectal cancers all over the world and has been reported to reduce mortality by 25% (4). Studies pointed out the sensitivity of FOBT between 12.9%-79.4% and the specificity between 86.7% and 97.7% (5).

The disadvantages of the FOBT are that it cannot differentiate between upper and lower gastrointestinal bleeding and the test may be affected by diet. On the other hand, FOBT is used in the first place in screening programs in our country because it is easily applicable and cost-effective.

In this study, we aimed to evaluate the colonoscopic and pathological findings of patients who underwent colonoscopy in our hospital due to positive FOBT and to discuss with the literature.

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MATERIAL AND METHOD

Patient Selection

Patients who referred to the endoscopy unit of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital for colonoscopy with a positive FOBT between January 2019- June 2021 were included in this study. The study was approved by the Health Sciences University, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee (Date: 14.07.2021, Decision No: 2021/180) and all procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with inadequate colon cleansing, active hematochezia, history of colon surgery or inflammatory bowel disease, and those with erosions, ulcers and malignant lesions in the upper gastrointestinal tract were excluded from the study.

Food intake (radish, turnip, broccoli, meat products, cabbage, cauliflower, apple, banana, iron therapy and vitamin C, etc.) that could increase the probability of false positive results was avoided before the test. The stool sample was collected in a clean, lidded container. Patients with diarrhea and women with vaginal bleeding were excluded.

Fecal Occult Blood Test and Colonoscopy

FOBT was performed with the Guaiac method. Guaiac reaction is a chemical method using indicators such as orthotoluidine, orthodonicidine and benzidine, and can detect bleeding of less than 10 ml. Colonoscopies were performed after appropriate preparation and terminal ileum was also evaluated. Biopsy was obtained when there was any pathology and polypectomy was performed if polyp was detected. Age, gender, colonoscopic findings and pathology results of the patients were noted.

Statistical Analysis

SPSS statistical program version 21.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation) were used to evaluate study data. Continuous variables were examined with Kolmogorov-Smirnov test for normal distribution. The differences between the two groups were examined with the Mann-Whitney U test or student T test. $p<0.05$ was considered statistically significant.

RESULTS

A total of 223 patients were included in the current study. Of the patients, 101 (45.3%) were male, 122 (54.7%) were female, with a mean age of 53.2 (18-90 years) (**Table 1**). Endoscopic diagnoses were as; polyps 49 (22%), colon cancer 13 (5.8%), inflammatory bowel disease 4 (1.8%), diverticulum 15 (6.7%), perianal disease 63 (28.3%) and normal colonoscopic findings 79 (35.4%).

Table1. Demographic data and colonoscopic findings of patient group

	n=223	%
Gender		
Male	101	45.3
Female	122	54.7
Age, mean		
53.2 (min 18 max 90)		
Colonoscopy findings		
Polyp	49	22.0
Presence of malignancy	13	5.8
Inflammatory bowel disease	4	1.8
Diverticulum	15	6.7
Perianal disease	63	28.3
Normal findings	79	35.4

The pathological features of patients with colon polyps were as tubular adenoma in 51%, tubulovillous adenoma in 18.4%, serrated adenoma in 2%, and hyperplastic polyp 28.6%.

In terms of dysplasia, 10.2% of the polyps had high grade and 28.6% had low grade dysplasia. The localizations of polyps and tumors according to their frequency were as; sigmoid colon (n=26, 41.9%), transverse colon (n=10, 16.1%), rectum (n=9, 14.5%), ascending colon(n=6, 9.7%), descending colon (n=6, 9.7%) and cecum (n=5, 8.1%), respectively. There was one polyp in 61.2%, two polyps in 20.4%, three polyps in 6.1%, four polyps in 4.1%, and five or more polyps in 8.2% of the patients (**Table 2**).

Table 2. Characteristics of colon polyps

	n=49/223	%
Pathology of polyp		
Tubular	25	51.0
Tubulovilloz	9	18.4
Serrated	1	2.0
Hyperplastic	14	28.6
Presence of dysplasia		
None	30	61.2
Low grade	14	28.6
High grade	5	10.2
Localization (polyps+tumors)		
Cecum	5	8.1
Ascending colon	6	9.7
Transverse colon	10	16.1
Descending colon	6	9.7
Sigmoid colon	26	41.9
Rectum	9	14.5
Total	62	100.0
The size of the polyp		
< 0,5 cm	24	49.0
<1 cm	22	44.9
<2 cm	1	2.0
<3 cm	2	4.1
Number of polyps		
1	30	61.2
2	10	20.4
3	3	6.1
4	2	4.1
≥ 5	4	8.2

When the colonoscopy findings of patients over and less than 50 years of age compared; polyps (p=0.01) and diverticulum (p=0.001) were significantly higher in patients over 50 years of age, while perianal diseases (p=0.031) and normal colonoscopic findings (p=0.008) were higher in patients younger than 50 years of age (**Table 3**).

Table 3. Comparison of colonoscopy findings of patients according to age groups

	>50 years (n=128, %)	<50 years (n=95, %)	p
Gender			0.273
Male	62 (61.4%)	39 (38.6%)	
Female	66 (54.1%)	56 (45.9%)	
Colonoscopy findings			<0.001*
Polyp	36 (73.5%)	13 (26.5)	0.01*
Presence of malignancy	10 (76.9%)	3 (23.1%)	0.142
Inflammatory bowel disease	2 (50%)	2 (50%)	0.763
Diverticulum	15 (100%)	0 (0%)	0.001*
Perianal disease	29 (46%)	34 (54%)	0.031*
Normal findings	36 (45.6%)	43 (54.4%)	0.008*

*p<0.05 was considered statistically significant.

DISCUSSION

FOBT is a test that indicates bleeding originating from any point of the gastrointestinal tract. This test is commonly used to investigate the etiology of anemia or in colon cancer screening programs. Through screening the asymptomatic population; prevention of gastrointestinal cancer, reduction of mortality, radical treatment of precancerous lesions and detection of early-stage cancers can be achieved (6). There are studies showing that mortality and morbidity decrease with colorectal cancer screening programs (7). Although the sensitivity and specificity of the FOBT is not very high, people over 50 years (40 years in some countries) scanned once in a year/ two years, and individuals with a family history of colon cancer have this test done at earlier ages. When FOBT is positive, endoscopic evaluation should be performed.

In the literature, FOBT studies include data from individuals from population-based colon cancer screening programs and mostly reflect the detection rates of precancerous lesions and colorectal cancers. In our study, the FOBT was requested both for the detection of colon cancer and precursor lesions, as well as pathologies leading to chronic blood loss such as subclinical inflammatory bowel disease and diverticulum as an inexpensive, easily applicable method.

Large randomized studies conducted in North America and Western Europe and observational studies from different parts of the world have shown that FOBT reduces mortality of colorectal cancer by 9-32% (8). In a 14-year prospective cohort study involving 30.381 patients from Japan, a 44% decrease in deaths due to colorectal cancers was reported with two or three consecutive FOBT screenings (9). Current guidelines on this subject recommend individuals aged 50-75 years to be screened with FOBT at two-year intervals and with colonoscopy at 10-year intervals (10). On the other hand, there is also evidence showing that screening with FOBT at two-year intervals has no effect on reducing the incidence of colorectal cancer (8).

In the studies from our country; Utku et al. (7) found 7.5% colorectal cancer and 26.2% polyps in the colonoscopy of patients with positive FOBT. Mayir et al. (11) detected 31.5% adenomatous polyps in screened individuals. Akkuzu et al. (12) reported 5.7% adeno-carcinoma, 19% adenomatous polyp, and 1.4% rectal malignant melanoma in screened patients. In another study in Turkey, precancerous adenomatous polyps were noted as 40% and colorectal cancer as 4% in FOBT positive patients (13).

When the localizations of tumors and polyps were examined, more than 50% of the lesions were detected in the rectum and sigmoid colon. This finding of the current study was compatible with the literature (8, 14-15). There are molecular differences between right-sided and left-sided colon tumors and sidedness of the colorectal cancers are important, especially in the metastatic behaviour and in response to anti-EGFR drugs.

One other significant finding of the present study was the high rate of polyps and diverticulum observed in people older than 50 years of age and this outcome was consistent with the literature (16). Potential benefits, potential risks of screening, and available resources should be considered for desicion-making of which age group to screen. For example, because the prevalence of colorectal cancers increase with age, maximum cost-effectiveness can be achieved by screening an older cohort of patients if resources are limited. However, this must be balanced with the number of patients who would be overlooked. Modeling packages were used to balance and analyze these factors. In the US, two modeling tools (MISCAN and SimCRC) were used in 2009 and concluded that screening should be done from age of fifty with annual FOBT and 10-year colonoscopy, or FOBT in 2-3 years plus rectosigmoidesoscopy in 5 years. An analysis including fecal immunochemical test and computed tomography colonoscopy in 2016 investigated the option of a longer screening interval (15 years colonoscopy) combined with an earlier screening start (at 45 years) option, but no significant evidence was found (16). On the other hand, there are also studies stating that the incidence of colorectal cancer increases at younger ages and that screening should be done at earlier ages (17-19).

In the current study, FOBT was requested in patients younger than 50 years of age with diagnostic indications such as iron deficiency. Perianal diseases and normal colonoscopic findings were found to be significantly higher in this group than the group of over 50 years of age. In a meta-analysis study conducted by Lee et al. (20) it was reported that the sensitivity of FOBT was low in indications other than colorectal cancer screening.

There were limitations in this study. First, it was retrospective. Second, the current study was involving one tertiary center. Prospective, multicenter large cohort studies including FOBT and new methods of colorectal cancer screening are needed to elucidate new perspectives to these methods over population. In this context, there are new methods being investigated for colorectal cancer screening such as analysis of methylated Septin 9 DNA in serum, multitarget-stool DNA or several DNA-RNA or protein markers (8).

CONCLUSION

Colon pathology was detected in approximately 2/3 of the patients presenting with a positive stool occult blood test. This test is an inexpensive, easily applicable method that helps to detect colon cancer and precursor lesions, as well as pathologies such as subclinical inflammatory bowel disease and diverticulum causing chronic blood loss.

FOBT should be used particularly in the community-based screening programs of asymptomatic individuals in our country as in European countries, due to its cost-effectiveness and easy access. However, when considered on an individual case to case basis, a negative FOBT should not interfere with colonoscopy screening

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Health Sciences University, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee (Date: 14.07.2021, Decision No: 2021/180).

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. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol 2021; 14: 101174.
2. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet 2019; 394: 1467-80.
3. TC SB Halk Sağlığı Genel Müdürlüğü Kolorektal Kanser Tarama Programı Ulusal Standartları. https://hsgm.saglik.gov.tr/tr/kanser-tarama-standartlari/listesi/kolorektal-kanser-tarama-program%C4%B1-ulusal-standartlar%C4%B1.html (access date: 08.08.2021).
4. Bretthauer M. Evidence for colorectal cancer screening. Best Pract Res Clin Anaesthesiol 2010; 24: 417-25.
5. Lieberman DA. Clinical practice. Screening for colorectal cancer. N Engl J Med 2009; 361: 1179-87.
6. Kara M, Tanoglu A. Screening strategies in a global public health issue colorectal carcinoma and place of colonoscopy. TAF Prev Med Bull 2013; 12: 743-50.
7. Utku OG, Ergul B, Oguz D. Gaitada gizli kan testi pozitifliği nedeni ile kolonoskopi yapılan hastaların kolonoskopik ve patolojik sonuçlarının değerlendirilmesi. Akademik Gastroenteroloji Derg 2018; 17: 17-20.
8. Lauby-Secretan B, Vilahur N, Bianchini F, et al. The IARC perspective on colorectal cancer screening. N Engl J Med 2018; 378: 1734-40.
9. Tanaka K, Sobue T, Zha L, et al. Effectiveness of screening using fecal occult blood test and colonoscopy on the risk of colorectal cancer: The Japan Public Health Center-based prospective study. J Epidemiol 2021; 10.2188/jea.JE20210057.
10. Qaseem A, Crandall CJ, Mustafa RA, et al. Screening for colorectal cancer in asymptomatic average-risk adults: a guidance statement from the American College of Physicians. Ann Intern Med 2019; 171: 643-54.
11. Mayir B, Ensari CÖ, Durhan A, Çöpelci Y. Kolorektal kanser tarama amaçlı yapılan gaytada gizli kan testi pozitif saptanan hastalarda kolonoskopi bulguları. Turk J Colorectal Dis 2018; 28: 27-30.
12. Akkuzu MZ, Sezgin O, Üçbilek E, et al. Gaitada gizli kan pozitifliği nedeniyle kolonoskopi yapılanlarda kolorektal malignite sıklığı. MKÜ Tıp Derg 2020; 11: 109-12.
13. Kara Y, Sarıcı İŞ, Kalaycı MU. Bölgemizde yürütülen kolon kanser tarama programının etkinliğinin değerlendirilmesi. İstanbul Kanuni Sultan Süleyman Tıp Derg 2019; 11: 31-6.
14. Hultcrantz R. Aspects of colorectal cancer screening, methods, age and gender. J Intern Med 2021; 289: 493-507.
15. Kamis F, Tanoglu A, Unal Cetin E, Beyazit Y, YazganY. Retrospective analysis of patients underwent colonoscopic polypectomy: A two-center study. Med Sc 2020; 9: 473-7.
16. Bevan R, Rutter MD. Colorectal cancer screening-who, how, and when? Clin Endosc 2018; 51: 37-49.
17. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013. J Natl Cancer Inst 2017; 109: djw322.
18. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut 2019; 68: 1820-6.
19. Saad El Din K, Loree JM, Sayre EC, et al. Trends in the epidemiology of young-onset colorectal cancer: a worldwide systematic review. BMC Cancer 2020; 20: 288.
20. Lee MW, Pourmorady JS, Laine L. Use of fecal occult blood testing as a diagnostic tool for clinical indications: a systematic review and meta-analysis. Am J Gastroenterol 2020; 115: 662-70.

Original Article

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Comparison of trans-articular Kirschner wire fixation and TightRope System for the treatment of acromioclavicular joint injuries

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ABSTRACT

Aim: Acromioclavicular joint (ACJ) injuries are common among the young and middle-aged population. The management of Grade 3 to 6 ACJ injuries is still controversial. The purpose of the present study was to compare the clinical results and complication rates of trans-articular Kirschner (K) wire fixation and the TightRope System for surgically treated ACJ injuries.

Material and Method: Patients with Grade 3 to 6 ACJ injuries surgically treated for acute ACJ injuries were included in this retrospective study. The patients were grouped according to the fixation method; the patients treated with the TightRope System were called Group 1 (n=17). The patients treated with trans-articular K-wire fixation were called Group 2 (n=21). The American Shoulder and Elbow Surgeons (ASES), Constant-Murley (CS), Visual Analog Scale (VAS) scores, and shoulder range of motion (ROM) values were evaluated, and the complications were recorded and compared between the two groups.

Results: Thirty-eight patients (7 females, 31 males) were included in the study with a mean age of 33±9.04. There was no significant difference between the two groups in terms of demographic and preoperative variables. ASES (P=0.400), CS (P=0.172), VAS (P=0.234), and ROM values were similar between the two groups. The rate of complications was significantly higher in Group 2 (P=0.025).

Conclusion: Trans-articular K-wire fixation and the TightRope System have similar clinical scores and ROM values; on the other hand, trans-articular K-wire fixation has significantly higher complication rates.

Keywords: Acromioclavicular joint, injury, surgical treatment, Kirschner wire, TightRope

INTRODUCTION

The acromioclavicular joint (ACJ) is a synovial joint that connects the clavicle to the shoulder blade; its injury accounts for approximately 9% of shoulder girdle injuries and is about five times more common in men than in women (1). Acromioclavicular joint dislocation (ACJD) occurs mainly during sports activities, while direct trauma to the adducted arm, falling on the shoulder directly forcefully. The treatment of these injuries depends on the degree of dislocation, patient complaints, and the period after the injury (2). The joint stability is assessed by clinical evaluation and conventional radiography. Classification is according to the Rockwood system, which defines six degrees of injury (3). This classification is based on the degree of disruption of the acromioclavicular and coracoclavicular ligaments and surrounding facial tissues and the degree of radiological displacement of the clavicle in relation to the acromion. Higher degrees are associated with more displacement and more severe ligament injury. Recently, the literature supports the nonsurgical management of Grade I and II injuries, and it is generally accepted that patients with Grade IV, V, and VI injuries benefit from operative treatment. However, optimal treatment for Grade III injuries remains controversial (4). There are numerous procedures and protocols designed to treat the AC joint, and the literature on treatment options is full of descriptions of surgical techniques (1,5). Therefore, there is no consensus on the treatment of AC joint dislocation, which continues to be controversial.

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Our study aimed to contribute to the literature by evaluating and comparing the clinical and radiological results of patients who underwent the trans-articular K-Wire fixation and the TightRope System technique in ACJD.

MATERIAL AND METHOD

After obtaining approval by Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (Date: 05.05.2021, Decision No: 278) and All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Patients who received surgical treatment for ACJD between January 2017 and January 2020 were evaluated using a retrospective database. Inclusion criteria included patients over 18 years of age, Grade III, IV, V, and VI acromioclavicular joint dislocations, acute dislocations (less than three weeks), and at least 1-year follow-up. Exclusion criteria were patients under 18 years of age, previous shoulder surgery on the ipsilateral side, systemic diseases affecting joint movement, grade 3 and 4 shoulder joint osteoarthritis, Grade I and II acromioclavicular joint dislocations of the same side, chronic dislocation independent from the grade (longer than 3 weeks), presence of ipsilateral neurologic disorder and follow-up period less than 1 year.

A total of 69 patients were identified for the study; 31 patients were excluded because they did not meet the criteria, and baseline data were lacking. Ultimately, 38 patients undergoing surgical treatment for ACJD met the inclusion criteria and had their data available for research.

Demographic and medical variables such as age, gender, operated side, dominant side, injury mechanism, type of dislocation, the time between injury and surgery, follow-up time, complications, and clinical and radiologic outcomes were all assessed.

Clinical and Radiological Evaluation

The anteroposterior and axillary radiographs of the shoulder were evaluated by an independent clinician to classify the types of dislocations and radiological evaluation at the last follow-up examination. Classification of dislocations was made according to the Rockwood classification (6). Weighted stress radiographs were used to differentiate type II ACJD from occult type III injury (7). While evaluating the radiological results, the vertical distance between the lower border of the acromion and the clavicle was compared with the contralateral side. The differences were measured in millimeters. Less than 2 mm, anatomical repositioning; 2-4 mm, slight loss reduction; 4-8 mm, partial reduction loss; more than 8 mm was considered complete reduction loss (8). At the last follow-up, the American Shoulder and Elbow Surgeons (ASES) (9), Constant-Murley (9), Visual Analog Scale (VAS) scores, and shoulder range of motion degrees were all assessed for clinical evaluation.

Surgical treatment of Grade III ACJD was applied to patients younger than 60 years of age, active, and with a higher activity level, depending on the experience and preferences of the surgeons. Two different surgeon were performed the operations. According to their own experience, one of the operating surgeons chose to use the trans-articular K-wire fixation for ACJD and the other to use the TightRope system. Therefore, in our study, the patients operated with the TightRope system were classified as Group 1, and the patients operated with the transarticular K-wire as Group 2.

Surgical Technique

All patients were given a single dose of 1 g cefazolin antibiotic intravenously 30 minutes before surgery, and they were operated on in the beach-chair position.

TightRope System

An invasive application was performed from the craniodorsal of the clavicle to the ventral border of the coracoid. The clavicle was pierced with a K-wire targeting the coracoid base. The clavicle and coracoid were drilled with a 4 mm diameter drill guided with a K-wire. The TightRope® system (Arthrex, Napoli, USA) was pulled using guide sutures. The endobutton was inverted under the caudal direction of the coracoid, and the fixing button was placed in the clavicle after reduction. The procedures performed were checked by fluoroscopy. Distal clavicle resection was not performed.

Trans-articular K-Wire Fixation

Using a frontolateral approach parallel to the clavicle, the insertion point for the K-wires was set, and the clavicle was repositioned. Two K-wires with a diameter of 2 mm were drilled lateral to the acromion and placed in parallel under fluoroscopic control targeting the cranial cortical of the clavicle. Metal cerclage was used in addition to the K-wires, and fixation was achieved. Removal of the implant was routinely performed 12 months after surgery, but earlier implant removal was performed in patients with implant failure earlier than 12 months during follow-up. Reoperations for implant failure or any revisions were analyzed as 'reoperations.' Routine implant removal procedures were not analyzed as 'reoperation.'

Rehabilitation

Patients have been used a sling for the postoperative six weeks. Passive mobilization and pendulum exercises were applied at first two weeks. Active abduction and flexion were allowed up to 30 degrees after two weeks and gradually increased to 90 degrees within six weeks. The full active movement was allowed at postoperative 8th week. After 3rd month muscle strengthening exercises were started.

Statistics

The mean, standard deviation, and percent values were used, as appropriate, to describe the data. The distribution for each measured variable was evaluated for normality using the Kolmogorov–Smirnov test. Categorical variables are summarized as frequency (n) and a percentage of the total. Statistical analyses were conducted with the $\chi 2$ test to compare categorical variables and the Student t-test or Mann Whitney U test to analyze group differences in clinical scores and the shoulder range of motion values. All statistical analyses were performed using the SPSS v24 (SPSS Inc., Armonk, NY) software. P values <0.05 were considered to be statistically significant.

RESULTS

The mean follow-up period was 35.28 ± 13.92 months (range 12-60) for all patients. Mean 34.56±15.72 (range, 12-60) months in Group 1 and 36±12.48 (range, 24-60) months in Group 2 without a statistical difference (p=0.204). Patient characteristics and distribution of demographic values between groups are presented in **Table 1.** When the preoperative dislocation degree was evaluated, 20 (52.6%) patients had grade III, 5 (13.2%) patients had grade IV, and 13 (34.2%) patients had grade V ACJD. The distribution between the two groups was not statistically significant in terms of the degree of dislocation (p=0.972)

Table 2 shows the comparison of ASES, CM, VAS scores, and shoulder range of motion degrees between both groups. Although mean ASES, CM, VAS scores were higher in Group 1 than Group 2 at the last examination, differences were not statistically significant (p=0.400, p=0.172, p=0.234, respectively). Both ROM measurements were also better in Group 1 without statistical significance (p=0.204, p=0.439, respectively). Complications were as follows, 3 (17.6%) patients had implant failure in Group 1, and 7 (33.3%) patients had implant failure in Group 2. (4 (19%) implant failure, 1 (4.8%) superficial infection, 1 (4.8%) osteolysis, 1 (4.8%) arthrosis). Complication rates were significantly higher in Group 2 (p=0.025).

Reoperation was performed in 1 (5.9%) patient in Group 1, and 4 (19.0%) patients in Group 2 (p=0.043). The reduction quality of the last follow-up examination was similar between Groups 1 and 2 (**Table 2**) (p=0.323).

Table 1. Demographic and disease-specific characteristics of the patients

Variable	Entire study population	Group 1	Group 2	p
Patient number, n (%)	38 (100)	17 (44.7)	21 (55.3)	
Age, year, (mean±SD [min-max])	33±9.04 (19-57)	32.23±8.74 (19-53)	33.61±9.45 (20-57)	0.966
Gender, n (%)				0.912
Female	7 (18.5)	3 (17.6)	4 (19.1)	
Male	31 (81.5)	14 (82.4)	17 (80.9)	
Side, n (%)				0.618
Right	24 (63.1)	10 (58.8)	14 (66.7)	
Left	14 (36.9)	7 (41.2)	7 (33.3)	
Dominant side, n (%)				0.796
Yes	21 (55.3)	9 (52.9)	12 (57.1)	
No	17 (44.7)	8 (47.1)	9 (42.9)	
Time from injury to surgery, days, (mean SD)	4.10±2.26 (1-11)	4.05±1.95 (2-9)	4.14±2.53 (1-11)	0.835
Injury mechanism, n (%)				0.875
Simple fall	10 (26.4)	4 (23.5)	6 (28.6)	
Traffic accident	14 (36.8)	7 (41.2)	7 (33.3)	
Sport trauma	14 (36.8)	6 (35.3)	8 (38.1)	

Abbreviations: SD: standard deviation, n: number, p<0.05 was defined as significant and defined in bold

Table 2. Clinical Scores, shoulder range of motion degrees, and radiologic reduction status of both groups

Variable	Entire Study Population	Group 1	Group 2	p
ASES, (mean±SD)	81.71±8.81	85.17±6.52	78.90±9.56	0.400
CM, (mean±SD)	80.47±8.36	83.58±6.53	79.95±8.96	0.172
VAS (mean±SD)	2.42±1.91	1.70±1.26	3.0±2.16	0.234
ROM, (mean±SD)				
Forward flexion	159.94±18.80	165.23±13.54	155.66±21.54	0.204
Abduction	153.28±27.16	160.11±19.77	147.76±31.31	0.439
Radiologic reduction assessment				
Anatomic reduction	22 (57.9)	12 (70.6)	10 (47.6)	0.323
Mild reduction loss	5 (13.2)	2 (11.8)	3 (14.3)	
Partial reduction loss	8 (21.1)	2 (11.8)	6 (28.6)	
Total reduction loss	3 (7.9)	1 (5.9)	2 (9.5)	

Abbreviations: SD: standard deviation, n: number, p<0.05 was defined as significant and defined in bold

DISCUSSION

The most important finding in our study was that there was no significant difference in the clinical, functional, and radiological results of patients with ACJD treated using K-wire fixation with tension band cerclage and the TightRope system.

One of the most common surgical techniques used to treat ACJD is K-wire fixation (10). In studies conducted on this subject, Sirveaux et al. (11) published long-term functional results of surgical treatment with K-wire fixation with tension band cerclage in 29 patients and obtained good and excellent results. Leidel et al. (10) achieved satisfactory functional results in short, midterm, and long-term follow-up with joint transfixation using K-wire fixation with tension band cerclage of Grade III ACJD. Murphy et al. (12) reported good and excellent clinical results in fixation results with K-wire fixation with tension band cerclage in the short-term follow-up of 23 patients with ACJD. Vrgoč et al. (13) compared K-wire fixation with tension band cerclage and TightRope System methods for surgical treatment of Grades III and V ACJD. They reported good clinical results in terms of surgical outcomes between patients and found no statistically significant difference. In a retrospective analysis of the results of Grade V ACJDs treated with K-wire fixation with tension band cerclage and screw stabilization for at least 15 years, successful functional results were obtained, and minor differences between the two groups were found (14). A recent study found no significant difference in ACJD surgical treatment between patients treated with K-wire fixation with tension band cerclage, the Weaver-Dunn procedure, single TightRope®, or double TightRope® (15). A biomechanical study showed that ACJ trans-articular K-wire fixation with tension band cerclage provided good mechanical resistance to secondary joint dislocation during passive motion (16). Studies have stated that satisfactory results can be obtained using K-wire fixation with tension band cerclage in ACJD repair. Still, the displacement of the wires poses the most critical risk in this method (4).

Our study observed loosening of the K-wire, displacement, and associated implant failure in 4 (19%) patients. Patients with implant failure were reoperated, and their K-wires and cerclage were removed. We obtained satisfactory clinical, functional, and radiological results in this method, but implant failure posed a serious risk for migration.

The TightRope technique is a stable and functional anatomical reconstruction procedure, and studies are showing that it results in forces equal to or even higher than the natural ligaments (17). Biomechanical studies have shown that the Tightrope system is superior to established surgical methods in treating ACJD and is stronger than natural coracoacromial ligaments. However, they have also been found to fail easily with cyclic loading, although clinical trials on this topic are infrequent (18-21).

Using the TightRope system for ACJD, Thiel et al. (22) obtained satisfactory functional results in the vast majority of patients. Still, in the same study, they found a fixation failure rate of 16.6%. Beris et al. (23) obtained satisfactory functional and radiographic results in treating Grade III and IV ACJD with the TightRope system in an average 18-month follow-up of 12 patients. In recent studies, the TightRope® system technique is an effective method to stabilize acute ACJD. In the results, encouraging data were obtained in high-grade ACJD (Grades IV - V) and Grade III dislocations (15). When the literature was reviewed, it was observed that ACJD surgical treatment had changed significantly in the last decade, the use of the previously popular K-wire techniques has decreased (from 37% in 2001 to 6% in 2014), while the TightRope® system is now used more frequently (27% in 2014) (15). As mentioned in the literature, satisfactory results have been achieved in both methods. Our study's data also reached higher shoulder scores and fewer pain scores in the surgical treatment performed with the TightRope technique. Still, there was no statistically significant difference in both determinations. In this respect, the data of our study is consistent with the literature.

Most of the complications after using Kirschner wires have been reported in the literature due to loss of reduction, posttraumatic osteoarthritis, clavicular osteolysis, superficial wound infections, and displacement of the wire to the lung, spinal cord, or longitudinal cord (7,24,). However, the TightRope technique has some disadvantages. It requires bicortical holes that can cause fractures in the clavicle and coracoid (17). Walz et al. (18) reported three coracoid fractures and one clavicle fracture in their study. Motta et al. (26) reported a loss of reduction in four cases (20%) of TightRope fixation due to the rupture of the sutures during the follow-up. Scheibel et al. (27) examined 27 patients who underwent TightRope fixation and reported mild reduction losses up to six months postoperatively. In other studies, fixation failure was reported in one-third of Grade III and V ACJD patients using the TightRope system (22,28). When the complications were evaluated in our study, we did not encounter wire displacement in any of the patients who underwent K-wire fixation with tension band cerclage. We attribute this result to regular patient follow-up and our routine removal of implants in the early period. Implant failure rates were similar in both groups, but the complication rates were significantly higher in the K-wire fixation group when evaluated together with other complications. We can attribute this result to the K-wires piercing and partially destroying the ACJ during application.

There are some limitations to our study. The first of these was the retrospective evaluation of the patients; the second was evaluating the results of relatively few patients; our third and last limitation was the evaluation of the results of two different surgeons. Examining the results of a single experienced surgeon can provide more precise data on the results. Beside that short follow-up time may lead to more subjective outcomes.

CONCLUSION

We achieved similar clinical, functional, and radiological results in both techniques, but we found more frequent complication rates in fixations made with K-wires. For this reason, we can say that the fixation method with TightRope is a safer technique in terms of complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (Date: 05.05.2021, Decision No: 278).

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. Mazzocca AD, Arciero RA, Bicos J. Evaluation and treatment of acromioclavicular joint injuries. Am J Sports Med. 2007; 35: 316-29.
2. Lafosse L, Baier GP, Leuzinger J. Arthroscopic treatment of acute and chronic acromioclavicular joint dislocation. Arthroscopy. 2005; 21: 1017.
3. Alyas F, Curtis M, Speed C, Saifuddin A, Connell D. MR imaging appearances of acromioclavicular joint dislocation. Radiographics. 2008; 28: 463-79.
4. Modi CS, Beazley J, Zywiel MG, Lawrence TM, Veillette CJ. Controversies relating to the management of acromioclavicular joint dislocations. Bone Joint J. 2013; 95: 1595-602.
5. Beitzel K, Cote MP, Apostolakos J, et al. Current concepts in the treatment of acromioclavicular joint dislocations. Arthroscopy. 2013; 29: 387-97.
6. Gorbaty JD, Hsu JE, Gee AO. Classifications in Brief: Rockwood Classification of Acromioclavicular Joint Separations. Clin Orthop Relat Res. 2017; 475: 283-7.
7. Johansen JA, Grutter PW, McFarland EG, Petersen SA. Acromioclavicular joint injuries: indications for treatment and treatment options. J Shoulder Elbow Surg. 2011; 20: 70-82.
8. Pavlik A, Csépai D, Hidas P. Surgical treatment of chronic acromioclavicular joint dislocation by modified Weaver-Dunn procedure. Knee Surg Sports Traumatol Art. 2001; 9: 307–12.
9. Wylie JD, Beckmann JT, Granger E, Tashjian RZ. Functional outcomes assessment in shoulder surgery. World J Orthop. 2014; 5: 623-33.
10. Leidel BA, Braunstein V, Kirchhoff C, Pilotto S, Mutschler W, Biberthaler P. Consistency of long-term outcome of acute Rockwood grade III acromioclavicular joint separations after K-wire transfixation. J Trauma. 2009; 66: 1666-71.
11. Sirveaux F, Traversari R, Roche O, Mole D. Outcome more than ten years after surgical treatment of acromioclavicular disjunction. J Bone Joint Surg Br. 2001; 83: 36.
12. Murphy M, Connolly P, Murphy P, McElwain JP. Retrospective review of outcome post open reduction and K-wire fixation for grade III acromioclavicular joint subluxations. Eur J Orthop Surg Traumatol. 2004; 14: 147-50.
13. Vrgoč G, Japjec M, Jurina P, et al. Operative treatment of acute acromioclavicular dislocations Rockwood III and V-Comparative study between K-wires combined with FiberTape(®) vs. TightRope System(®). Injury. 2015; 46: 107-12.
14. Virtanen KJ, Remes VM, Tulikoura IT, et al. Surgical treatment of Rockwood grade-V acromioclavicular joint dislocations: 50 patients followed for 15–22 years. Acta Orthop. 2013; 84:191-5.
15. Horst K, Garving C, Thometzki T, et al. Comparative study on the treatment of Rockwood type III acute acromioclavicular dislocation: Clinical results from the TightRope® technique vs. K-wire fixation. Orthop Traumatol Surg Res. 2017; 103: 171-6.
16. Fialka C, Michlits W, Stampfl P, et al. Biomechanical analysis of different operative techniques for complete acromioclavicular joint disruptions. Osteosynthesis and Trauma Care. 2005; 13: 154-9.
17. Cai L, Wang T, Lu D, Hu W, Hong J, Chen H. Comparison of the Tight Rope Technique and Clavicular Hook Plate for the Treatment of Rockwood Type III Acromioclavicular Joint Dislocation. J Invest Surg. 2018; 31: 226-33.
18. Walz L, Salzmann GM, -Fabbro T, Eichhorn S, Imhoff AB. The anatomic reconstruction of acromioclavicular joint dislocations using 2 TightRope devices: a biomechanical study. Am J Sports Med. 2008; 36: 2398–406.
19. Nuchtern JV, Sellenschloh K, Bishop N, et al. Biomechanical evaluation of 3 stabilization methods on acromioclavicular joint dislocations. Am J Sports Med. 2013; 41: 1387-94.
20. Zooker CC, Parks BG, White KL, Hinton RY. TightRope versus fiber mesh tape augmentation of acromioclavicular joint reconstruction: a biomechanical study. Am J Sports Med. 2010; 38: 1204-8.
21. Ladermann A, Gueorguiev B, Stimec B, Fasel J, Rothstock S, Hoffmeyer P. Acromioclavicular joint reconstruction: a comparative biomechanical study of three techniques. J Shoulder Elbow Surg. 2013; 22: 171-8.
22. Thiel E, Mutnal A, Gilot GJ. Surgical outcome following arthroscopic fixation of acromioclavicular joint disruption with the tightrope device. Orthopedics. 2011; 34: 267-74.
23. Beris A, Lykissas M, Kostas-Agnantis I, Vekris M, Mitsionis G, Korompilias A. Management of acute acromioclavicular joint dislocation with a double-button fixation system. Injury. 2013; 44: 288-92.
24. Fraser-Moodie JA, Shortt NL, Robinson CM. Injuries to the acromioclavicular joint. J Bone Joint Surg Br. 2008; 90: 697-707.
25. Hackenburch W, Regazzoni P, Schwyzer K. Surgical treatment

of lateral clavicular fracture with the clavicular hooked plate. Z. Unfallchir. Versicherungsmed. 1994; 87: 145-52.

26. Motta P, Maderni A, Bruno L, Mariotti U. Suture rupture in acromioclavicular joint dislocations treated with flip buttons. Arthroscopy. 2011; 27: 294-8.

27. Scheibel M, Droschel S, Gerhardt C, Kraus N. Arthroscopically assisted stabilization of acute high-grade acromioclavicular joint separations. Am J Sports Med. 2011; 39: 1507–16.

28. Defoort S, Verborgt O. Functional and radiological outcome after arthroscopic and open acromioclavicular stabilization using a doublebutton fixation system. Acta Orthop Belg. 2010; 76: 585–91.

Original Article

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Pediatric palliative care: data of the first 13 months of operation

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ABSTRACT

Aim: Children with complex chronic conditions are main candidates for pediatric palliative care (PPC). Despite the proven advantages of palliative care for these children, the literature lacks on the adequate description of the pediatric population receiving this care. The aim of this study was to describe demographic characteristics of the patients, to examine the patient survival and the factors affecting patient survival. To our knowledge, this is the first description of the cohort of children and adolescents on PPC in Turkey.

Material and Method: This retrospective chart review study examined patients receiving palliative care at Health Sciences University, Dr. Sami Ulus Maternity and Children's Training and Research Hospital and Children's Training and Research Hospital between 2.12.2019 and 31.12.2020. The data of demographics, underlying diagnosis, medical technology dependence, symptoms at admission, number of hospitalizations, number of emergency department (ED) admissions were collected.

Results: 70 male and 66 female patients were admitted 259 times during the observation period. The median length of hospital stay was 7 days. Median age at referral was 44 months (range:2.7-215). Fifty-one patients (37.5%) were younger than 2 years of age. Neurological diseases were the most prevalent disease group. 56 of our patients (41%) had a tracheostomy. 82 patients (60.3%) needed respiratory support. Fifty of them were ventilated through home-type mechanical ventilator. Only 28 patients (20.6%) could be fed through oral route. Nasogastric tube (n=84, 61.8%) was the main device used by children who needed nutritional support. 52% of patients were referred from ED. Most prevalent symptoms of the patients at admission were dyspnea and tachypnea. 151 of the patients (58.3%) were diagnosed with infection, the most common infection was lower respiratory tract infection (n=103, 39.8%). Of 259 PPC center admissions 224 (86.5%) were discharged to home. Twenty-seven children (20%) died during study period. Nineteen of deceased patients died in intensive care unit (70%). The 1-year survival rate of the patients was 78.1%. In logistic regression analysis the risk of death was 3.4 times higher in patients ≤2 years of age (CI: 1.4-8.8, p=0.01) and in patients with respiratory support (CI: 1.1-11.0, p=0.04).

Conclusion: Describing the cohort of patients on PPC provides important information on the complexity of their disease process, types of their illnesses, medical technology dependence, re-admission rates, mortality status and factors affecting mortality. Important research has been done but pediatric palliative care is still in infancy in Turkey. Future prospective research is needed to understand the unique challenges of PPC.

Keyword: End of life, medical devices, multiple chronic health conditions, survival

INTRODUCTION

With the improvement of medical science and care, a growing number of children are living with complex and often life-limiting chronic conditions (1). Children with complex chronic conditions (CCC), including cancer, congenital conditions, neuromuscular, hematological diseases, necessitate the use of multiple therapies and patients with these conditions represent the main pediatric candidates for palliative care (2). These children require intense medical and nursing care in the home and often lengthy hospital stays. Earlier studies found that palliative care results in higher parent satisfaction, better symptom management, higher quality of life, and often longer life; however, the current literature about adequate description of the pediatric population receiving this care is scarce (3-7).

We examined data from all children referred to pediatric palliative care (PPC) center from 2 December 2019 to 31 December 2020, at one children's hospital in Ankara. The palliative care program at this hospital began in 2th December 2019. The center provides

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24/7 in-hospital care. The purpose of this study was to describe demographic characteristics, to describe the types of illnesses that resulted in referral, to examine the patient survival following referral to palliative care and to examine the relationship between patient survival and key clinical and sociodemographic variables. To our knowledge, this is the first description of the cohort of children and adolescents on PPC in Turkey.

MATERIAL AND METHOD

Research Design

This retrospective chart review study examined patients receiving palliative care at Health Sciences University, Dr. Sami Ulus Maternity and Children's Training and Research Hospital during a 13-months period. A cohort was created by examining records of all patients referred to PPC center during the study period from December 2, 2019, through December 31, 2020. Children were included in the cohort if they were between the ages of 1 month and 18 years when they received the referral to PPC.

Procedures

Inpatient data were retrieved from the electronic medical record of our hospital. All data were identified before analysis. The study was approved by the Dr. Sami Ulus Maternity and Children's Training and Research Hospital Clinical Researchs Ethics Committee (Date: 04.02.2021, Decision No: E-21/02-96). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Measurement

The data collected included gender, date of birth, date of death, date of referral to palliative care, underlying diagnosis, technology dependence, symptoms at admission, the date of hospitalization, the date of discharge, the reason for hospitalization, therapies during hospitalization, the number of hospitalizations during the study period, the number of ED admissions, and the number of home health care admission.

Children were grouped based on their ages into 4 groups: ages 0 to 2 years, ages 3-5 years, ages 6–10 years, and ages 11-18 years. The underlying diagnoses were collapsed into categories as neurological disorders, metabolic disorders, syndromes, cardiological disorders, prematurity and other according to Feudtner's CCC categories (2). The cause of PPC center admission was grouped as training/adaptation for new medical condition of the children, lower respiratory system infections, sepsis, increased seizure frequency, other infections, gastrointestinal system problems, electrolyte and kidney function disorders and other conditions. The primary outcome variable was the total number of days from referral to palliative care until death or the end of the study. Right censoring occurred if a child survived beyond the end of the study period. For children who survived beyond the end of the study period, the total number of days was calculated using the end of the study (December 31, 2020).

Data Analyses

All data analyses were conducted using IBM SPSS Statistics v20 with $p < 0.05$ as the significance level. Descriptive statistics were computed to characterize the sample, including gender and age distribution, survival status, and admission reason. Comparison of binary variables was performed with the Chi square test. Continuous values were expressed as median [min-max, interquartile range (IQR)]. Kaplan–Meier estimation was used to estimate the survival function during study period using first admission to PPC center as starting point. Group comparison was performed with log-rank test. Logistic regression model was used to find the factors affecting death and hospital readmissions.

RESULTS

Demographic and Clinical Properties of the Cohort

In the study period, the PPC center cared for 136 patients. Seventy (51.5%) patients were male. Median age at referral was 44 months (min:2.7 max:215, IQR:97.3 months). Fifty-one patients (37.5%) were younger than 2 years of age. Neurological diseases were the most prevalent disease group. Place of residency of fifty-one patients (37.5%) was outside Ankara. **Table 1** shows demographic variables of the patients. 56 of our patients (41%) had a tracheotomy. 82 patients (60.3%) needed respiratory support. Fifty of them were ventilated through home type mechanical ventilator. Only 28 patients (20.6%) could be fed through oral route. Nasogastric tube (n=84, 61.8%) was the main device used by children who needed nutritional support (**Table 1**).

Hospital Admissions

136 patients were admitted 259 times in total. The median length of hospital stay was 7 days (min:1, max:108 IQR:22 days). Fifty-one patients (37.5%) had more than once PPC center admissions. Only six admissions were planned for symptom control by PPC team. Other admissions were referred to PPC center from emergency departments (ED), intensive care units (ICU) or from other inpatient services. More than half of the admissions (n=135, 52.1%) were referred from ED. **Table 2** demonstrates the clinical characteristics of all admissions. Most prevalent symptoms of the patients at admission were dyspnea/tachypnea/low oxygen saturation in 85 patients (32.8%) and fever in 81 patients (31.3%) (**Table 2**). Most of the patients (n=151, 58.3%) were diagnosed with infection, the most common infection was lower respiratory tract

infection (n=103, 39.8%) (**Table 2**). Antibiotics were used in 206 (79.5%) admissions. More than one antibiotic was administered in 150 admissions. In 82 admissions antiepileptics of the patients were revised. Oral opioids (morphine) were started only in 3 patients.

Table 1. The demographics of the patients

	N=136
Female/male	70 / 66
Median age (month) (IQR)	44 (97.3)
Age groups	
0-2 years age group	51 (37.5%)
3-5 years age group	25 (18.4%)
6-10 years age group	36 (26.5%)
>11 years age group	24 (17.6%)
Underlying diseases	
Neurological disorders (n, %)	72 (52.9%)
Epilepsy	23
Cerebral palsy	21
Central nervous system malformations	14
Neurodegenerative disease	5
Spinal muscular atrophy	3
Demyelination disorders	6
Metabolic disorders (n, %)	34 (25%)
Amino acid metabolism disorders	9
Mitochondrial diseases	7
Lysosomal storage disorders	6
Fatty acid oxidation disorders	4
Glycogen storage diseases	2
Urea cycle disorders	2
Mucopolysaccharidoses	2
Rare metabolic disorders	2
Syndromes (n, %)	19 (14%)
Down syndrome	3
Jeune syndrome	2
Miscellaneous	14
Cardiovascular disorders (n, %)	5 (3.7%)
Ventricular septal defect	2
Tetralogy of Fallot	2
Coarctation of the aorta	1
Prematurity (n, %)	4 (2.9%)
Other disorders (n, %)	2 (1.5%)
Immune deficiencies	1
Primary ciliary dyskinesia	1
Place of residency	
Ankara	85 (62.5%)
Outside Ankara	51 (37.5%)
Status of having respiratory support	
No respiratory support	54 (39.7%)
Respiratory support via free flow oxygen	23 (16.9%)
Respiratory support via Bilevel Positive Airway Pressure	9 (6.6%)
Respirator support via home-type mechanical ventilator	50 (36.8%)
Status of having nutritional support	
No nutritional support	28 (20.6%)
Nutritional support via nasogastric tube	84 (61.8%)
Nutritional support via gastrostomia	24 (17.6%)

Table 2. The characteristics of the hospital admissions

Total hospital admissions	N=259
The patient was referred to PPC center from*	
Emergency Department	135 (52.1%)
PICU	62 (23.9%)
NICU	7 (2.7%)
Other inpatient services	49 (18.9%)
Number of admissions	
1 admission	85 (62.6%)
2 admissions	22 (16.3%)
3 admissions	9 (6.7%)
4 admissions	9 (6.7%)
5 admissions	3 (2.3%)
6 admissions	3 (2.3%)
8 admissions	2 (1.5%)
9 admissions	2 (1.5%)
Prevalent symptoms of the patients at admission	
dyspnea/tachypnea/low oxygen saturation	85 (32.8%)
fever	81 (31.3%)
irritability	53 (20.5%)
convulsions	42 (16.2%)
vomiting	35 (13.5%)
increased spasticity	27 (10.4%)
dysuria	11 (4.2%)
diarrhea	10 (3.9%)
edema	6 (2.3%)
Causes of hospitalization in PPC patients*	
Lower respiratory tract infection	103 (39.8%)
training/adaptation of the family for new medical condition of the children	57 (22%)
Sepsis	26 (10%)
Other infections (urinary tract infection, cellulitis)	22 (8.5%)
Increased frequency of epileptic seizures	21 (8.1%)
Gastrointestinal system problems (vomiting, diarrhea)	19 (7.3%)
Electrolyte and kidney function test disorders	6 (2.3%)
Other	5 (1.9%)

*6 admissions were planned for symptom control by PPC team

Of 259 PPC center admissions 224 (86.5%) were discharged to home. Eighteen of them worsened during their PPC care admission and were transferred to intensive care. 13 of them were transferred to other hospitals. 4 of them died during their PPC care admission.

Fifty-one of the patients (37.5%) had more than once PPC center admissions. Multiple PPC center admissions were more prevalent in patients ≤2 years of age compared to patients > 2 years of age (49% to 30.6%, p=0.03). In logistic regression analysis being ≤2 years of age, having respiratory or nutrition support did not affect having multiple PPC center admissions.

Follow up and Patient Survival

Median duration of care was 9.5 months (min:0.2 max:13, IQR:6.2 months). After their discharge from PPC center, 33 of our patients (24.3%) were followed up by the home health services unit of our hospital. 58 (42.6%) of our patients had no ED visit. 78 patients had at least one ED-visit. During the observation period, 11 patients (8%) had more than ten ED visits.

Twenty-seven children (20%) died during study period. The majority of deceased patients died in intensive care unit (n=19, 70%). The place of death was PPC center in 4 patients, ED in 2 patients and home in 2 patients. The 1-year survival rate of our patients was 78.1%. **Figure 1** shows Kaplan-Meier Survival curve of our cohort. Median age at the time of death was 12.2 months (min:3.5, max:221.1; IQR:38.9 months). The mortality rate was significant higher in patients ≤ 2 years of age compared to patients > 2 years of age (n=18, 35.3% to n=9, 10.6%) (p <0.01). 1-year survival of patients was 56.8% in patients ≤2 years of age and 86.6% in patients > 2 years of age (p <0.01) (**Figure 2A**). One-year survival was significant higher in patients without respiratory support than in patients with respiratory support (87.1% to 68.1%; p<0.01) (**Figure 2B**). In logistic regression analysis the risk of death was 3.4 times higher in patients ≤2 years of age (CI: 1.4-8.8, p=0.01) and in patients with respiratory support (CI: 1.1-11.0, p=0.04).

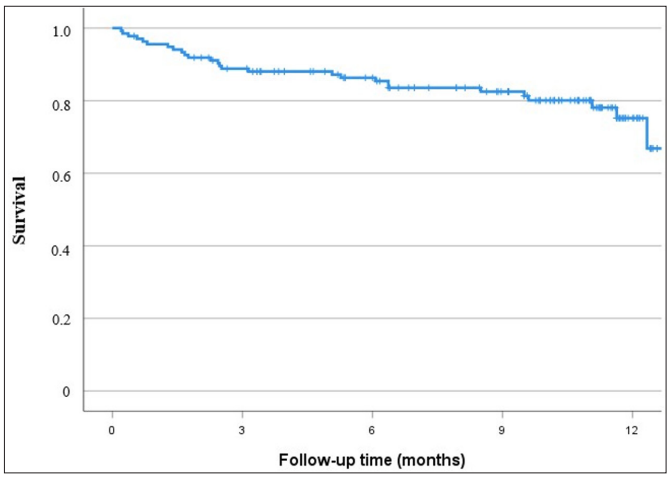

Figure 1. Kaplan-Meier Survival curve of the 136 patients.

DISCUSSION

This study examined total hospitalizations in PPC centre of Dr. Sami Ulus Maternity and Children's Training and Research Hospital between December 2019 and December 2020. To our knowledge, this is the first survey in Turkey that defined the demographic and clinical characteristics of patients on PPC. We found that, the patients had high medical technology dependence, they admitted primarily to ED for their symptoms, had low utility of home-health care services. Infections were the major cause of hospitalizations. One-fifth of the cohort died in the follow-up time. The place of death was ICUs in 70 %.

The most common underlying diagnoses seen in this study were neurologic and metabolic diseases. We had no malignancy patients that referred to our center. Consistent with our study, neurological conditions are reported to be the leading underlying diagnoses in the US (8, 9), the UK (10), Canada (11) and Italy (12, 13). The explanation of high rate of metabolic disease in this study could be the higher incidence of consanguine marriages in our country (14). The underrepresentation of malignancy children was noteworthy in this cohort. PPC is an emerging subspecialty in Turkey like the other developing countries in the world (15). We can speculate that the rate of malignancy patients will increase with the improved awareness of other pediatric subspecialties about PPC.

The high utilization of medical technology described in our study is much higher than other studies. Approximately 60% and 80% of our cohort needed respiratory and nutritional support, respectively. 56 of our patients (41%) had a tracheostomy. Amarri et al. reported very recently that 9% and 11% of their cohort needed tracheostomy and mechanical ventilation in their cohort (13). Feudtner et al. reported tracheostomy rate as 10.1% and mechanical ventilator rate as 8.5% in their multi-center prospective

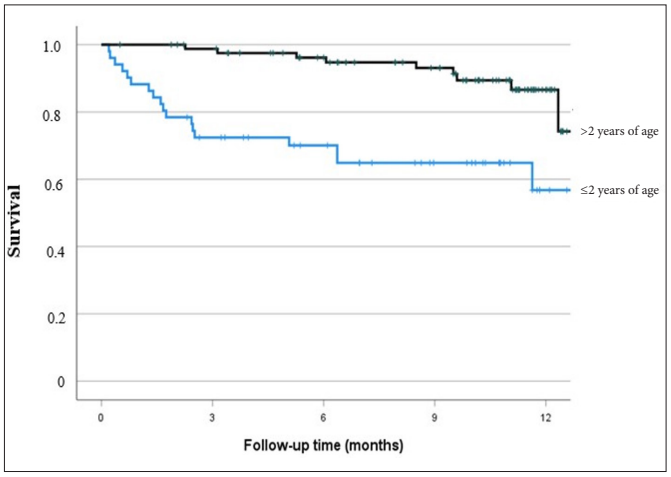

Figure 2A. Kaplan-Meier Survival curve of the 136 patients classified according to age. Patients who were ≤2 years of age had significant worse survival than patients >2 years of age.

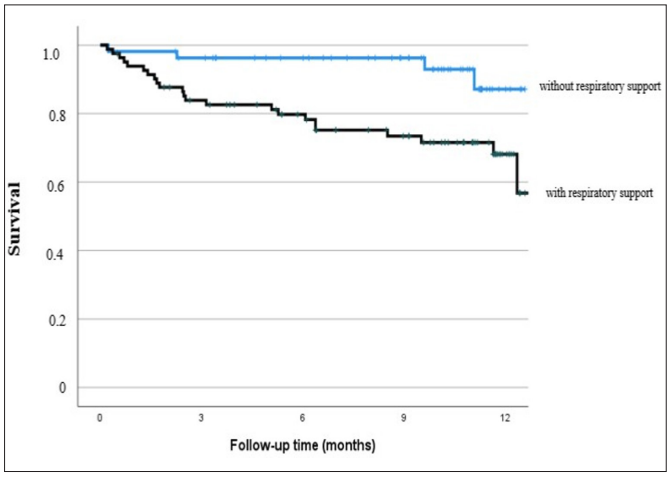

Figure 2B. Kaplan-Meier Survival curve of the 136 patients classified according to respiratory support. Patients with respiratory support had significant worse survival than patients without respiratory support.

study (8). The high rate of medical technology dependence in our cohort may be the result of the lack of legal basis of withhold or withdraw life support treatments in Turkey (16). In terms of cultural, religious and social aspects end-of-life (EOL) decisions are sensitive and challenging (17). Western countries have improved the EOL concept and they have established its ethicolegal framework (18, 19). New aspects and discussions about EOL concept are urgently needed in Turkey, as well.

Half of the patients in our cohort were referred to PPC center from ED. The core reason for ED admission was the respiratory symptoms. Children with multiple CCC and neurological impairment, together with the use of technological devices are known to have higher access to health services (20). It was shown that children with chronic conditions comprise a significant portion of annual pediatric ED visits. Additionally, they had increased length of stay at ED and hospital or PICU admission rate (21). The health system of Turkey has some specialties compared to western health systems. There is no ambulatory PPC program in Turkey. Only opportunity for these children is the home health care teams. They are not 24/7 available and not well integrated to palliative care system in Turkey, however. Because of these disadvantages only 24% of our cohort was followed by home health care service of our hospital. As a result, palliative care is provided by inpatient palliative care centers in Turkey. To date there are approximately 5500 palliative care beds in Turkey, of which only 129 belong to pediatric PPC centers. This low count of pediatric palliative beds shows an important demand on PPC centers in Turkey, since 27.2% of our population is under 18 years of age (22).

The cause of hospitalization was infections in 58% of the patients. The patients on PPC are at higher risk for colonization and infections with multidrug-resistant pathogens because of multiple hospital admissions, surgical interventions,frequent antibiotic treatments, presence of long-lasting devices (e.g., gastrostomy tube, tracheostomy), and their underlying condition (23). Acute lower respiratory tract infections can be life threatening in children with CCC (24). Therefore, strict adhering to infection control measures is even more vital in these patients.

Despite the lack of ambulant palliative care centers in Turkey we could discharge to home 86.5% of our patients with a median 7 days of hospital stay. In a multicenter adult study from our country, the rate of discharge to home was determined as 56.6% in inpatient palliative care setting (25). Since prognosis, life expectancy and functional outcome often less clear in PPC compared to adult palliative care setting (26), our parents prefer to be at home despite high burden of care work. The available literature shows that patients requiring PPC and their parents prefer to stay at home, but keeping such children at home is not easy to realize (8, 27-29). The caregivers must learn the skills needed to manage the young patient and they must improve their ability to handle the medical devices (27). All of this takes a great deal of effort and time. Caring for a child with such complex healthcare needs at home can negatively affect the physical and emotional well-being of parents, siblings and other members of the family (30). Therefore, to keep these children at home new planning in Turkish health care system should be made such as constant presence of trained personnel.

During the 13-month follow-up 27 patients (20%) died. One-year survival was 78.1%. One-year mortality rate is reported as 30-39% in the PPC literature (8, 9). Mortality rate reaches to 55% in 5 years in PPC settings (31). Mortality rates at adult PC units were reported to be between 23% and 78% in the literature, and the general mortality rate was expected to be ≤60–75% (25). The overall pattern of prolonged survival of patients who received PPC, and their multiple readmissions to hospital, show that PPC centers will provide health care service not only to new patients but also to a large group of established patients who have long surviving. Therefore, appropriate health care staffing for PPC teams needs to account, new as well as the existing patient cases (8). A majority of the deaths occurred in the acute care hospital setting in our study. This is similar to the data presented by Frissola and Feudnter et al. (8, 9). They explained their high rate of inpatient death with limited access to ambulant palliative care and inpatient hospice programs. We had no access to ambulant PPC and inpatients hospice programs in our country as well. The differences concerning the place of death may be due to cultural preferences (31). To our knowledge there is no study in our country about the preference of place of death in children with life-limiting chronic condition and their parents. Being younger than 2 years of age and having respiratory support are important risk factors of mortality. These children should be followed up more intensely and their parents should inform about early mortality.

CONCLUSION

Describing the cohort of patients on PPC provides important information on the complexity of their disease process, types of their illnesses, medical technology dependence, re-admission rates, mortality status and factors affecting mortality. Important research has been done but pediatric palliative care is still in infancy in Turkey. Research examining the needs of both children and their families with life-threatening illnesses is central for the quality of life of these children and their families. Future prospective research is needed to understand the unique challenges of PPC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Dr. Sami Ulus Maternity and Children's Training and Research Hospital Clinical Researchs Ethics Committee (Date: 04.02.2021, Decision No: E-21/02-96).

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. Bogetz JF, Schroeder AR, Bergman DA, Cohen HJ, Sourkes B. Palliative care is critical to the changing face of child mortality and morbidity in the United States. Clin Pediatr 2014; 53: 1030-1.
2. Feudtner C, Hays RM, Haynes G, Geyer JR, Neff JM, Koepsell TD. Deaths attributed to pediatric complex chronic conditions: national trends and implications for supportive care services. Pediatrics 2001; 107: e99-e.
3. Austin L, Luker K, Caress A, Hallett C. Palliative care: community nurses' perceptions of quality. BMJ Quality Safety 2000; 9: 151-8.
4. Davies B, Collins JB, Steele R, Cook K, Brenner A, Smith S. Children's perspectives of a pediatric hospice program. J Palliat Care 2005; 21: 252-61.
5. Good PD, Cavenagh J, Ravenscroft PJ. Survival after enrollment in an Australian palliative care program. J Pain Symptom Manage 2004; 27: 310-5.
6. Johnston DL, Nagel K, Friedman DL, Meza JL, Hurwitz CA, Friebert S. Availability and use of palliative care and end-of-life services for pediatric oncology patients. J Clin Oncol 2008; 26: 4646-50.
7. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non–small-cell lung cancer. N Engl J Med 2010; 363: 733-42.
8. Feudtner C, Kang TI, Hexem KR, et al. Pediatric palliative care patients: a prospective multicenter cohort study. Pediatrics 2011; 127: 1094-101.
9. Frizzola M, Miller EG. Referrals to a new pediatric palliative care team: details of the first 12 months of operation. J Palliat Med 2014; 17: 585-8.
10. Fraser LK, Miller M, Hain R, et al. Rising national prevalence of life-limiting conditions in children in England. Pediatrics 2012; 129: e923-e9.
11. Widger K, Davies D, Drouin DJ, et al. Pediatric patients receiving palliative care in Canada: results of a multicenter review. Arch Pediatr Adolesc Med 2007; 161: 597-602.
12. Benini F, Trapanotto M, Spizzichino M, Lispi L, Pozza LVd, Ferrante A. Hospitalization in children eligible for palliative care. J Palliat Med 2010; 13: 711-7.
13. Amarri S, Ottaviani A, Campagna A, De Panfilis L. Children with medical complexity and paediatric palliative care: a retrospective cross-sectional survey of prevalence and needs. Ital J Pediatr 2021; 47: 1-7.
14. Koc I, Eryurt MA. The causal relationship between consanguineous marriages and infant mortality in Turkey. J Biosoc Sci 2017; 49: 536.
15. Downing J, Powell RA, Marston J, et al. Children's palliative care in low-and middle-income countries. Arch Dis Child 2016; 101: 85-90.
16. Baykara N, Utku T, Alparslan V, Arslantaş MK, Ersoy N. Factors affecting the attitudes and opinions of ICU physicians regarding end-of-life decisions for their patients and themselves: A survey study from Turkey. PloS one 2020; 15: e0232743.
17. Saeed F, Kousar N, Aleem S, et al. End-of-life care beliefs among Muslim physicians. Am J Hosp Palliat Care 2015; 32: 388-92.
18. Bell D. The legal framework for end of life care: a United Kingdom perspective. Intensive Care Med 2007; 33: 158-62.
19. Vincent J-L. End-of-life practice in Belgium and the new euthanasia law. Intensive Care Med 2006; 32: 1908-11.
20. Cohen E, Berry JG, Camacho X, Anderson G, Wodchis W, Guttmann A. Patterns and costs of health care use of children with medical complexity. Pediatrics 2012; 130: e1463-e70.
21. O'Mahony L, O'Mahony DS, Simon TD, Neff J, Klein EJ, Quan L. Medical complexity and pediatric emergency department and inpatient utilization. Pediatrics 2013; 131: e559-e65.
22. İstatistiklerle Çocuk, 2020 20.04.2021. Available from: https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Cocuk-2020-37228.
23. Schmidt P, Hasan C, Simon A, Geffers C, Wager J, Zernikow B. Multidrug-resistant bacteria in a paediatric palliative care inpatient unit: results of a one year surveillance. GMS Hyg Infect Control 2020; 15.
24. Burton C, Vaudry W, Moore D, et al. Burden of seasonal influenza in children with neurodevelopmental conditions. Pediatr Infect Dis J 2014; 33: 710-4.
25. Göksel F, Şenel G, Oğuz G, et al. Development of palliative care services in Turkey. Eur J Cancer Care 2020; 29: e13285.
26. WHO. Integrating palliative care and symptom relief into paediatrics: a WHO guide for health-care planners, implementers and managers 2018.
27. Lazzarin P, Schiavon B, Brugnaro L, Benini F. Parents spend an average of nine hours a day providing palliative care for children at home and need to maintain an average of five life-saving devices. Acta Paediatr 2018; 107: 289-93.
28. Elias ER, Murphy NA. Home care of children and youth with complex health care needs and technology dependencies. Pediatrics 2012; 129: 996-1005.
29. Vickers JL, Carlisle C. Choices and control: parental experiences in pediatric terminal home care. J Pediatr Oncol Nurs 2000; 17: 12-21.
30. Hauer J. Identifying and managing sources of pain and distress in children with neurological impairment. Pediatr Ann 2010; 39: 198-205.
31. Bender HU, Riester MB, Borasio GD, Führer M. "Let's bring her home first." Patient characteristics and place of death in specialized pediatric palliative home care. J Pain Symptom Manage 2017; 54: 159-66.

Original Article

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Sonographic evaluation of intra-abdominal organs in children with familial Mediterranean fever

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ABSTRACT

Objective: The reticuloendothelial system is rarely assessed in patients with familial Mediterranean fever (FMF). We aimed to evaluate the size of the liver and spleen by ultrasonography in children and adolescents with FMF and compare it to their healthy peers.

Material and Method: Patient data were evaluated by height, weight, and age and compared with those of healthy controls.

Results: A total of 86 children with FMF diagnosed using the Turkish Pediatric Criteria and 54 healthy children were included. The extent of splenomegaly was 27.9% in the FMF group. The mean spleen length was 99.84±17.4 mm in patients and 93.44+15.49 mm in controls (p=0.03). The mean liver length was 122.61±17.4 mm in patients and 117.71±16.04 mm in controls (p=0.104). FMF appears to affect spleen length independently of anthropometric data (t=2.182; p=0.031). Splenomegaly was accompanied by the M694V (32.55%, n=17) and E148Q (3.4%, n=3) mutations.

Conclusion: FMF affects spleen length independently of anthropometric data. Splenomegaly may reflect subclinical inflammatory activity in FMF patients in remission. Spleen size can serve as a marker of subclinical inflammation during remission.

Keywords: Familial Mediterranean fever, ultrasonography, splenomegaly, children, inflammatory markers.

INTRODUCTION

Familial Mediterranean fever (FMF) is an acute, repetitive, and self-limiting autoinflammatory disease inherited in an autosomal-recessive manner and characterized by fever and abdominal, joint, and chest pain (1). FMF is caused by mutations in the MEFV gene located on the short arm of chromosome 16. The MEFV gene encodes pyrin, a genetic defect that increases the inflammatory response (2). Many MEFV mutations have been reported. Colchicine halts or limits FMF attacks in most patients and prevents the development of amyloidosis, which is the most serious complication (3). Few studies have explored the effects of FMF on the reticuloendothelial system (4). Splenomegaly, hepatomegaly, and lymphadenopathy have been reported in FMF patients (5,6). Here, we measured the spleen and liver sizes of children with FMF who were in remission, as well as of healthy controls.

MATERIAL AND METHOD

The study was approved by the Gaziosmanpaşa University Clinical Researchs Ethics Committee (Date: 03.01.2016, Decision No: 16-KAEK-060). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 86 FMF patients diagnosed using the Turkish pediatric criteria and 54 healthy children were included (7). Patients who had congenital anomaly, connective tissue diseases, metabolic, renal, endocrine and infectious diseases were excluded from the present study. Disease severity was determined using the modified Pras scoring system (8). Sonographic measurements of the liver and spleen were obtained during symptom-free periods by a radiologist with 10 years of experience using the Toshiba Aplio 500 platform (Toshiba Medical Systems, Tokyo, Japan) and 3.5-MHz pvt-375BT Convex Probe. Spleen

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measurements were made with subjects supine in a slightly right lateral decubitus position. The spleen was measured between the superomedial and inferolateral boundaries. Liver measurements were made in the supine position. The longitudinal axis was measured on the midclavicular plane. The upper edge (under the diaphragm dome) served as the upper margin and the bottom edge as the lower margin. The data were evaluated with reference to height, weight and age standards and compared with those of healthy controls. Informed consent was obtained from all participants or their parents before inclusion.

Statistical Analysis

The data were evaluated using SPSS version 19 software.

RESULTS

Patient ages ranged from 3 to 17 years. A total of 49 (57%) were girls and 37 (43%) boys. The mean age of FMF patients was 11.1±3.77 years and that of controls 10.21±4.13 years (p=0.19). The mean body mass index of FMF patients was 18.01±4.1 kg/m² and that of controls 18.37±3.5 kg/m² (p=0.59). The average age at diagnosis was 7.49±3.94 years. The most common clinical findings were abdominal pain (87.2%, n=75), fever (74.4%, n=64), arthritis (62%, n=54), chest pain (30.2%, n=26), and an erysipelas-like rash (5.8%, n=5). The mean spleen length was 99.84±17.4 mm in FMF patients and 93.44±15.49 mm in controls (p=0.03). The mean liver length was 122.61±17.4 mm in patients and 117.71±16.04 mm in controls (p=0.104) (**Table 1**). The most common mutation was M694V (32.5%, n=28). Splenomegaly was often accompanied by M694V (32.55%, n=17) and E148Q mutations (3.4%, n=3).

Spleen size (as revealed by sonography) was affected by FMF, being 5.355 mm greater (with statistical significance) in FMF patients than in controls when spleen length was considered a dependent variable (t=2.182; p=0.031) (**Tables 2, 3**).

Statistical Analysis

Continuous variables are shown as means with standard deviations and categorical variables as numbers with percentages. The average values of quantitative variables were compared. Cross-tables and the chi-squared test were used to compare qualitative variables. Pearson correlation coefficients between quantitative variables were calculated. A p-value < 0.05 was considered to reflect statistical significance. Multivariate linear regression was used to explore the effects of selected variables on spleen and liver lengths. All calculations were made using IBM SPSS Statistics ver. 19 (SPSS Inc. and IBM Co., Somers, NY, USA).

Table 1. Demographic characteristics of FMF patients

Variables	Statistics
Age, years	10.76±3.9
Sex (M/F)	64 (45.7)/76 (54.3)
Weight, kg	38.06±17.7
Height, cm	140.59±22.0
BMI, kg/m²	18.15±3.87
FMF familial history	14 (16.3)
Appendectomy history	11 (12.8)
Age at onset (years)	6.05±3.8
Age at diagnosis (years)	7.49±3.9
Severity score	7.24±1.4
Liver length, mm	120.7±17.3
Spleen length, mm	97.4±18.1

Data are shown as means±standard deviation or as numbers (%).

Table 2. Effects of age, height, weight, BMI, and FMF on spleen and liver measurements

DV	IV	β	SD	t	p
Spleen	Age	0.914	0.954	0.958	0.340
	Weight	0.096	0.396	0.243	0.808
	Height	0.127	0.284	0.445	0.657
	BMI	0.703	1.028	0.684	0.495
	FMF	5.355	2.454	2.182	0.031*
Liver	Age	-0.31	0.873	-0.355	0.723
	Weight	-0.274	0.364	-0.754	0.452
	Height	0.682	0.261	2.612	0.010*
	BMI	1.117	0.944	1.183	0.239
	FMF	3.657	2.252	1.624	0.107

DV: dependent variable, IV: independent variable.
The effects of independent variables on dependent variables as revealed by a multivariate linear regression model. *The difference was statistically significant. Reference: control group.

Table 3. Bivariate correlations between qualitative variables

Variable			Weight (kg)	Height (cm)	BMI (kg/m²)
FMF	Liver	r	0.595	0.708	0.361
		p	<0.001	<0.001	0.001
	Spleen	r	0.587	0.586	0.432
		p	<0.001	<0.001	<0.001
Control	Liver	r	0.708	.659	0.535
		p	<0.001	<0.001	<0.001
		n	54	54	54
	Spleen	r	0.536	0.486	0.489
		p	<0.001	<0.001	<0.001

Pearson's correlation coefficients were calculated. BMI: body mass index. Statistically significant at p < 0.01.

DISCUSSION

FMF is a repetitive autoinflammatory disease. The most common symptoms are fever, abdominal pain, arthritis/arthralgia, and chest pain; more rarely, long-term febrile myalgia, erysipelas-like erythema, and orchitis are observed. FMF is associated with splenomegaly. However, the reticuloendothelial features of FMF have received little attention (4, 9). We evaluated spleen and liver sizes by age, height, and body weight in FMF patients during remission, and healthy controls.

The levels of acute-phase proteins such as CRP, ESR, and SAA increase in FMF patients during attacks and usually return to normal during remission (10). However, subclinical inflammation continues during remission (11,12), increasing the risks of anemia, splenomegaly, decreased bone mineral density, heart disease, and (especially) secondary amyloidosis (13, 14). Inflammation develops when certain cytokines are secreted by macrophages and monocytes (15).

The spleen is a platelet reservoir. Splenomegaly may be associated with increased hemolysis or may reflect a vascular, infectious, infiltrative, or inflammatory disorder. A significant correlation was evident between thrombocyte activation and splenomegaly in FMF children in remission. The mean platelet volume, which reflects platelet function and activation, was higher in FMF patients (16).

Splenomegaly extending past the Costa edge (i.e., > 5 cm) has been reported in approximately 30% of FMF patients. Splenomegaly was usually not associated with amyloidosis but was linked to chronic inflammation (17). Korkmaz et al. (18) detected splenomegaly in approximately 25% of FMF patients (without amyloidosis) during attack-free periods. Ultrasonography revealed splenomegaly in 27% of patients with acute attacks and 13% of asymptomatic patients, but hepatomegaly in only 13% of asymptomatic patients (19). Dursun et al. (20) reported splenomegaly in 27.9% of FMF children in remission. Our figures were similar.

The phenotype–genotype relationship of FMF has been investigated extensively (20-23). Moradian et al. (24) found that all mutations were associated with hepatomegaly and splenomegaly. Exon 10 mutations associated with severe disease phenotypes (polyserositis, erysipelas-like erythema, splenomegaly, and vasculitis) reflected high-level M694V penetration. A homozygous M694V mutation has been linked to splenomegaly (25). We found that splenomegaly was usually accompanied by M694V and E148Q mutations.

Previous studies demonstrated correlations of longitudinal measurements of the liver, spleen, and kidneys with other bodily parameters and defined normal organ sizes (26, 27). Our longitudinal measurements were in line with such findings. As age, height, and weight increased, the spleen and liver sizes also increased (28). Safak et al. (26) evaluated schoolchildren and found no significant difference in organ size according to sex. Organ size was most correlated with body weight. Similarly, we found that organ size increased with age, height, and weight and did not differ according to. Age, height, and weight affected both liver and spleen sizes in FMF patients. In the present study, FMF was the most important parameter affecting spleen length, thus more significant than age, height, or weight.

A diagnosis of FMF is based on clinical criteria. Elevations in the levels of acute phase reactants, indicative of inflammation, support diagnosis of an acute attack. Subclinical inflammation was apparent in 25% of patients in remission (20). Ultrasonography is useful for evaluating the features of both an acute attack and remission. Splenomegaly during remission is considered to herald the development of an acute attack (20).

CONCLUSION

The spleen and liver dimensions were correlated with age, height, and weight. FMF affected spleen size (compared with that of healthy controls). To the best of our knowledge, this is the first study to compare the abdominal organ sizes of FMF patients in remission to anthropometric measurements. Splenomegaly may reflect low-level inflammatory activity during remission. In FMF patients, spleen size can serve as a marker of subclinical inflammation during remission.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Gaziosmanpaşa University Clinical Researchs Ethics Committee (Date: 03.01.2016, Decision No: 16-KAEK-060).

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

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REFERENCES

1. Ozen S, Bilginer Y. A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. Nature Reviews Rheumatology 2014; 10: 135-47.
2. Yalcinkaya F, Cakar N, Acar B, et al. The value of the levels of acute phase reactants for the prediction of familial Mediterranean fever associated amyloidosis: a case control study. Rheumatology International 2007; 27: 517-22.
3. La Regina M, Ben Chetrit E, Gazparyan AY, Livneh A, Ozdogan H, Manna R. Current trends in colchicine treatment in familial Mediterranean fever. Clin Exper Rheumatol 2013; 31: 41-6.

4. Aharoni D, N Hiller, Hadas-Halpern I. Familial Mediterranean fever: abdominal imaging findings in 139 patients and review of the literature. Abdominal Imaging 2000; 25: 297-300.
5. Barakat MH, Karnik AM, Majeed HWA, El-Sobki NI, Fenech FF. Familial Mediterranean fever (recurrent hereditary polyserositis) in Arabs—a study of 175 patients and review of the literature. Q J Med 1986; 60: 837–47.
6. Inal A, Yilmaz, M Kendirli, SG, Altintas, DU. Karakoc, GB. The clinical and genetical features of 124 children with Familial Mediterranean fever: experience of a single tertiary center. Rheumatol Int 2009; 29: 1279–85.
7. Yalcinkaya F, Ozen S, Ozçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009; 48: 395-8.
8. Ozen S, Aktay N, Lainka E et al. Disease severity in children and adolescents with familial Mediterranean fever: a comparative study to explore environmental effects on a monogenic disease. Ann Rheum Dis 2009; 68: 246-8.
9. Rimon D, Meir Y, Cohen L, Retroperitoneal lymphadenopathy in familial Mediterranean fever. Postgrad Med J 1989; 65: 776-8.
10. Oncu K, Yazgan Y, Tanoglu A, et al; Can serum fetuin-A be regarded as an inflammatory marker among patients with familial Mediterranean fever? Dig Dis Sci 2013; 58: 3212-7.
11. Akyol T, Düzenli T, Tanoğlu A. Evaluation of serum CXC chemokine ligand 16 (CXCL16) as a novel inflammatory biomarker or familial Mediterranean fever disease. Turk J Med Sci 2021; 51: 813-8.
12. Lachmann H.J, Sengül B, Yavuzşen TU, et al; Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 2006; 45: 746-50.
13. Bilginer Y, Akpolat T, Ozen S. Renal amyloidosis in children. Pediatr Nephrol, 2011; 26: 1215-27.
14. Ben-Zvi I, Livneh A. Chronic inflammation in FMF: markers, risk factors, outcomes and therapy. Nat Rev Rheumatol 2011;7:105-12.
15. Baykal Y, Saglam K, Yilmaz MI, Taslipinar A, Akinci SB, Inal A. Serum sIL-2r, IL-6, IL-10 and TNF-alpha level in familial Mediterranean fever patients. Clin Rheumatol 2003; 22: 99-101.
16. Marzouk H, Lotfy HM, Farg Y, Rashed LA, El-Garf K. Mean platelet volume and splenomegaly as useful markers of subclinical activity in Egyptian children with Familial Mediterranean Fever: a cross-sectional study. Int J Chronic Dis 2015; 2015: 152616.
17. Livneh A, Langevitz P, Zemer D, et al. The changing face of familial Mediterranean fever. Semin Arthritis Rheum 1996; 26: 612-27.
18. Korkmaz C, Ozdogan H, Kasapçopur O, yazici H. Acute phase response in familial Mediterranean fever. Ann Rheum Dis 2002; 61:79-81.
19. Aharoni D, Hiller N, Hadas-Halpern I. Familial Mediterranean fever: abdominal imaging findings in 139 patients and review of the literature. Abdom Imaging 2000; 25: 297-300.
20. Dursun I, Gok F, Babacan O, et al. Are mean platelet volüme and splenomegaly subclinical inflammatory marker in children with familial Mediterranean fever? Health 2010; 2: 692–695.
21. Ureten K, Gönülalan G, Akbal E, et al. Demographic, clinical and mutational characteristics of Turkish familial Mediterranean fever patients: results of a single center in Central Anatolia. Rheumatol Int 2010; 30: 911-5.
22. Tunca M, Akar S, Onen F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 2005; 84: 1-11.
23. Dusunsel, R, Dursun I, Gündüz Z, et al. Genotype-phenotype correlation in children with familial Mediterranean fever in a Turkish population. Pediatr Int 2008; 50: 208-12.
24. Moradian MM, Sarkisian T, Amaryan G, et al. Patient management and the association of less common familial Mediterranean fever symptoms with other disorders. Genet Med 2014; 16: 258-63.
25. Koné Paut I, Dubuc M, Sportouch J, Minodier P, Garnier JM, Touitou I. Phenotype-genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneomucous features. Rheumatology (Oxford) 2000; 39: 1275-9.
26. Safak AA, Simsek E, Bahcebasi T. Sonographic evaluation of the normal limits and percentile curves of liver, spleen, and kidney dimensions in healthy school-aged children. J Ultrasound Med 2005; 24: 1359-64.
27. Konus OL, Ozdemir A, Akkaya A, Erbaş G, Celik H, Işik S. Normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography. AJR Am J Roentgenol 1998; 171: 1693-8.
28. Warnakulasuriya DTD, Pathirennahalage P, Peries UC, et al. Ultrasonographic parameters of the liver, spleen and kidneys among a cohort of school children in Sri Lanka. Bmc Pediatrics 2017; 17: 192.
29. Dogan TH, Başak M, Karatağ O, Değirmenci H, Ozkurt H. Sonographic evaluation of liver, spleen and kidney sizes in healthy children aged 0-14 years. Journal of Child Health and Diseases 2004; 47: 107-13

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Evaluation of hematological indices in terms of COVID-19 related mortality and ICU admission

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ABSTRACT

Introduction: The COVID-19 pandemic has shown that patients should be categorized according to their risk group, patient follow-up and the use of health resources should be arranged according to this categorization. Therefore, practical and inexpensive biomarkers are needed. In this study, the relationship between neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV) and red blood cell distribution width (RDW) levels, which can be easily calculated by complete blood count, with mortality and intensive care unit (ICU) admission in COVID-19 disease was evaluated.

Material and Method: 748 inpatients with positive COVID-19 PCR test were evaluated retrospectively. The NLR, PLR, MPV and RDW levels calculated from the complete blood count parameters of the patients at hospital admissions and their relationship with the mortality and the ICU admission in COVID-19 disease were evaluated.

Results: In terms of mortality, a statistically significant difference was found between RDW levels in the evaluation performed in the patient groups who survived and died (p: 0.014). No statistically significant difference was found in NLR, PLR and MPV levels. In the evaluation performed in the patient groups who were and were not referred to the intensive care unit, a statistically significant difference was found between the two groups in RDW and NLR levels (p: 0.042, p: 0.01, respectively). There was no statistically significant difference between PLR and MPV levels for ICU admission.

Conclusion: RDW level was found to be associated with COVID-19 related mortality and ICU admission.

Keywords: COVID-19, mortality, ICU admission

INTRODUCTION

After the SARS-Cov-2 virus was first detected in China in December 2019, it has spread to more than 100 million people in more than 200 countries, causing a global pandemic. The World Health Organization (WHO) declared an emergency in January 2020 and a pandemic on March 11, 2020, and the disease name was determined as COVID-19. COVID-19 is a disease that can progress in a broad spectrum from asymptomatic illness to severe lung disease (1,2). Inflammation and its control play an important role in the prognosis of viral pneumonias (3). Dysregulation of the immune response and uncontrolled inflammation are the main determinants of prognosis in COVID-19. Inflammation markers such as NLR PLR and potential predictors of viral infections have been confirmed to be associated with serious illness and mortality in COVID-19 (4,5). Lymphocytopenia is also a confirmed independent mortality risk factor in COVID-19 (6). Platelets play a critical role in the inflammatory response in addition to hemostasis, and platelet count and volume can change with infection (7). It has been shown that MPV changes in many clinical conditions such as sepsis, infective endocarditis and pneumonia (8). Anisocytosis is defined as volume heterogeneity in erythrocytes and is expressed as RDW (9). RDW has been shown to predict mortality in respiratory tract infections. In addition, RDW is associated with poor prognosis in sepsis (10). The COVID-19 pandemic has shown that patients should be categorized according to their risk group, patient follow-up and the use of health resources should be arranged

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according to this categorization. Therefore, practical and inexpensive biomarkers are needed. In this study, we evaluated the relationship between NLR, PLR, MPV and RDW levels, which can be easily calculated by complete blood count, with mortality and ICU admission in COVID-19 disease.

MATERIAL AND METHOD

The study was conducted retrospectively, using hospital medical records of patients with positive COVID-19 Real time PCR test and treated as inpatient at Health Sciences University Kanuni Sultan Süleyman Training and Research Hospital between September 1, 2020 and December 31, 2020. 748 patients were included in the study. Hemoglobin, neutrophil, lymphocytes, platelet, RDW, MPV levels at the hospitalization of the patients were recorded and evaluated. ICU admission and mortality due to the disease were recorded. The relationship between NLR, PLR, RDW and MPV levels with ICU admission and mortality was evaluated. Complete blood count parameters were determined by a hematology analyzer (mindray BC-6800Plus). Permission was obtained from the Ethics Committee of Health Sciences University Kanuni Sultan Süleyman Training and Research Hospital for the study (Date: 11.03.2021, Decision No: KAEK/2021.03.70) and the study is conducted in accordance with the Declaration of Helsinki.

Statistical Study

All analyses were performed using SPSS version 21.0 for Windows (IBM Inc, Chicago, Illinois, USA) and using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California, USA). The variables were investigated using visual (histograms) and analytical methods (Kolmogorov-Smirnov /Shapiro-Wilk tests) to determine whether or not they were normally distributed. Chi-square test was used for comparisons of categorical variables. Continuous variables were shown as mean ± standard deviation or median (interquartile range) according to their distribution pattern. Ordinal variables and continuous variables that do not have normal distribution were compared by the Mann-Whitney U test. The Student t-test was used to evaluate differences between the two groups in normally distributed continuous variables. A value of $p<0.05$ (2-sided) was considered statistically significant.

RESULTS

In our study, data of 748 patients with a total of 410 men and 338 women diagnosed with COVID-19 were analyzed. The mean age of the patients included in the study was 62.5±15.3. The data of the hematological parameters of the patients are presented in **Table 1**. In our study, the number of patients referred to the ICU was 68 (9.1%). The disease resulted in mortality in 47 (6.2%) of 748 patients. While the patients included in the study were grouped as survival and death in terms of mortality, they were grouped as patients who were referred to the intensive care unit or not, according to the intensive care admissions. Statistically significant difference was found between RDW levels in the evaluation of survival and death groups in terms of mortality (p: 0.014). For mortality, no statistically significant difference was found between the two groups in NLR, PLR and MPV levels (p: 0.12, p: 0.79 and p: 0.33, respectively). The clinical and laboratory parameters of the two patient groups classified according to mortality are presented in **Table 2**. In the evaluation performed in the patient groups who were and were not referred to the intensive care unit, a statistically significant difference was found between the two groups in RDW and NLR levels (p: 0.042, p: 0.01, respectively). There was no statistically significant difference between the PLR and MPV levels of the two groups (p: 0.79 and p: 0.17, respectively). Clinical and laboratory parameters in two patient groups classified according to ICU admission are given in **Table 3**.

Table 1. Hematological parameter data of all patients

	Patients (n:748)
Age	62.5±15.3
Female/Male (n)	338/410
WBC (10^3/μL)	7.4±3.4
Neutrophil (10^3/μL)	4.7 (3.3-7.0)
Lymphocyte (10^3/μL)	1.3±0.6
HGB (g/dL)	12.7±1.9
PLT (10^3/μL)	219±91
MPV (fL)	10±1.1
RDW (%)	13.4 (12.8-14.4)
NLR	4.0 (2.5-6.5)
PLR	170 (119-244)

Values are presented using means ± standard deviations for normally distributed and medians and first and third quartiles in the brackets for the non-normally distributed variables; WBC: White blood cell; HGB: Hemoglobin; PLT: Platelet; MPV: Mean platelet volume; RDW: Red blood cell distribution width; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio

Table 2. Laboratory data of survival and death groups

	Survival (n:701)	Death (n:47)	p
Gender F/M (n)	319/382	19/28	0.54
Age	61±15.1	74±12.7	0.001
WBC (10^3/μL)	7.4±3.4	7.6±3.9	0.71
Neutrophil (10^3/μL)	4.7 (3.3-7.0)	5.2 (3.2-7.4)	0.48
Lymphocyte (10^3/μL)	1.3±0.6	1.1±0.7	0.09
HGB (g/dL)	12.7±1.9	12.3±1.8	0.15
PLT (10^3/μL)	221±90	185±91	0.009
MPV (fL)	10.6±1.1	10.8±1.1	0.33
RDW (%)	13.4 (12.8-14.3)	13.8 (13.3-14.6)	0.014
NLR	4 (2.4-6.3)	4.3 (2.6-9.4)	0.12
PLR	172 (119-242)	157 (110-297)	0.79

Values are presented using means ± standard deviations for normally distributed and medians and first and third quartiles in the brackets for the non-normally distributed variables; WBC: White blood cell; HGB: Hemoglobin; PLT: Platelet; MPV: Mean platelet volume; RDW: Red blood cell distribution width; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio

Table 3. Laboratory parameters and demographic data of patient groups in terms of admission to the intensive care unit

	Patients referred to ICU (n: 68)	Patients not referred to ICU (n: 680)	p
Gender F/M	26/42	312/368	0.22
Age	71±13.1	61±15.2	0.001
WBC (10^3/μL)	7.6±3.4	7.4±3.4	0.59
Neutrophil (10^3/μL)	5.4 (3.5-7.3)	4.6 (3.3-7)	0.17
Lymphocyte (10^3/μL)	1.1±0.66	1.3±0.65	0.028
HGB (g/dL)	12.4±2	12.7±1.9	0.14
PLT (10^3/μL)	189±83	222±91	0.005
MPV (fL)	10.8±1.2	10.6±1.1	0.17
RDW (%)	13.8 (13.3-14.6)	13.4 (12.8-14.3)	0.014
NLR	4.8 (2.9-9.1)	3.8 (2.4-6.2)	0.011
PLR	165 (121-286)	171 (118-242)	0.79

Values are presented using means ± standard deviations for normally distributed and medians and first and third quartiles in the brackets for the non-normally distributed variables; WBC: White blood cell; HGB: Hemoglobin; PLT: Platelet; MPV: Mean platelet volume; RDW: Red blood cell distribution width; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio

DISCUSSION

The rapid spread of the disease in pandemic conditions requires categorizing patients according to risk groups, therefore regulating the patient follow-up and use of medical resources accordingly. Effective, practical and inexpensive biomarkers are needed for this grouping.

Thrombocytopenia is seen at a rate of 5-41% in the course of COVID-19 and is typically at the level of mild (100-150×10^9/L) thrombocytopenia (11). Low platelet count is associated with severe disease and mortality (12,13). This thrombocytopenia can be explained by clearance from the reticuloendothelial system, endothelial damage, platelet autoantibody formation, spleen and hepatic sequestration, and bone marrow megakaryocyte suppression (14).

Neutrophil is the major component of the leukocyte population and triggers humoral immunity by playing a role in the cellular response against the virus (15). It makes the production of virus-related inflammatory factors such as IL-6, IL-8 and TNF-alpha from endothelium and lymphocyte (16). The neutrophil levels are detected higher than normal in COVID-19 patients (17). Lymphocytopenia is associated with overactivation of the inflammatory cascade (18). Lymphocyte apoptosis develops due to increased TNF-alpha and IL-6 in cytokine storm, as well as COVID-19 disease down-regulates genes that cause T lymphocyte proliferation (19,20). Lymphocytopenia is detected in 80% of critically ill COVID-19 patients and 25% of mild disease (18,21).

In the literature, NLR and PLR are associated with severe disease in the course of COVID-19. In addition, a relationship has been shown between NLR with hospitalization time and mortality (16,22). According to these data, in our study, platelet and lymphocyte levels were significant for mortality, while the PLR level was not statistically significant, which can be explained by the co-occurrence of thrombocytopenia and lymphocytopenia in the course of COVID-19. In our study, while NLR level was not associated with mortality, it was found to be associated with ICU admission. Favipiravir, an antiviral drug also used in the treatment of COVID-19, can cause neutropenia (23). This limited association can be explained by the fact that the majority of the study group used favipiravir. In our study, MPV level was not found to be associated with mortality in the course of COVID-19, similar to the literature (24).

Proinflammatory cytokines such as TNF-alpha and IL-1 released in the cytokine storm due to COVID-19 reduce the level of erythropoietin and cause a change in the level of RDW (25). Disease-related hypoxia may also cause changes in RDW levels (26). SARS virus affects growth and apoptosis by directly affecting hematopoietic stem cells (27). Increase in the RDW level has been shown to be associated with both sepsis and mortality due to COVID-19 (28,29). In our study, similar to the literature, we found RDW level to be statistically significantly associated with mortality and ICU admission.

CONCLUSION

Risk grouping with simple and practical markers makes it easier to determine the patient follow-up and treatment approach in COVID-19. NLR, PLR, MPV and RDW are simple, inexpensive and reproducible tests calculated on complete blood count devices. Among these parameters, RDW level is associated with mortality and ICU admission due to COVID-19 disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: Permission was obtained from the Ethics Committee of Health Sciences University Kanuni Sultan Süleyman Training and Research Hospital for the study (Date: 11.03.2021, Decision No: KAEK/2021.03.70)

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. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-20.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
3. 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.
4. Xiang N, Havers F, Chen T, et al. Use of national pneumonia surveillance to describe influenza A(H7N9) virus epidemiology, China, 2004-2013. Emerg Infect Dis 2013; 19: 1784-90.
5. Wang R, He M, Yin W, et al. The Prognostic nutritional index is associated with mortality of COVID-19 patients in Wuhan, China. J Clin Lab Anal 2020; 34: e23566.
6. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020; 5: 33.
7. 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.
8. Güçlü E, Kocayiğit H, Okan HD, et al. Effect of COVID-19 on platelet count and its indices. Rev Assoc Med Bras (1992) 2020; 66: 1122-7.
9. Lippi G, Mattiuzzi C, Cervellin G. Learning more and spending less with neglected laboratory parameters: the paradigmatic case of red blood cell distribution width. Acta Biomed 2016; 87: 323-8.
10. Zhang L, Yu CH, Guo KP, Huang CZ, Mo LY. Prognostic role of red blood cell distribution width in patients with sepsis: a systematic review and meta-analysis. BMC Immunol 2020; 21: 40.
11. Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19. J Thromb Haemost 2020; 18: 1469-72.
12. 12.Li Q, Cao Y, Chen L, et al. Hematological features of persons with COVID-19. Leukemia 2020; 34: 2163-72.
13. Jiang SQ, Huang QF, Xie WM, Lv C, Quan XQ. The association between severe COVID-19 and low platelet count: evidence from 31 observational studies involving 7613 participants. Br J Haematol 2020; 190: e29-e33.
14. Wool GD, Miller JL. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology 2021; 88: 15-27.
15. Kusumanto YH, Dam WA, Hospers GA, Meijer C, Mulder NH. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis 2003; 6: 283-7.
16. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol 2020; 84: 106504.
17. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis 2020; ciaa270.
18. 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.
19. Mazzoni A, Salvati L, Maggi L, et al. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. J Clin Invest 2020; 130: 4694-703.
20. Ouyang Y, Yin J, Wang W, et al. Downregulated Gene Expression Spectrum and Immune Responses Changed During the Disease Progression in Patients With COVID-19. Clin Infect Dis 2020; 71: 2052-60.
21. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020; 71: 762-8.
22. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect 2020; 81: e6-e12.
23. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir - a potential treatment in the COVID-19 pandemic?. J Virus Erad 2020; 6 : 45-51.
24. Bommenahalli Gowda S, Gosavi S, Ananda Rao A, et al. Prognosis of COVID-19: red cell distribution width, platelet distribution width, and C-reactive protein. Cureus 2021; 13: e13078.
25. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. J Interferon Cytokine Res 1998; 18: 555-9.
26. Soliz J, Schneider-Gasser EM, Arias-Reyes C, et al. Coping with hypoxemia: Could erythropoietin (EPO) be an adjuvant treatment of COVID-19?. Respir Physiol Neurobiol 2020; 279: 103476.
27. Yang M, Li CK, Li K, et al. Hematological findings in SARS patients and possible mechanisms (review). Int J Mol Med 2004; 14: 311-5.
28. Hu ZD, Lippi G, Montagnana M. Diagnostic and prognostic value of red blood cell distribution width in sepsis: A narrative review. Clin Biochem 2020; 77: 1-6.
29. Foy BH, Carlson JCT, Reinertsen E, et al. Association of red blood cell distribution width with mortality risk in hospitalized adults with SARS-CoV-2 infection. JAMA Netw Open 2020; 3: e2022058.

Original Article

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Antibiotic resistance of *Enterococcus* species: 3-year data

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ABSTRACT

Aim: The aim of this study was to investigate the prevalence of *Enterococcus* species and to evaluate susceptibilities to antimicrobial agents in a state (secondary) hospital.

Material and Method: A total of 1676 enterococci strains (490 *E. faecium*, 1146 *E. faecalis*, 10 *E. casseliflavus*/*E. gallinaru*m and 30 other *Enterococcus* species) isolated from cultures obtained from January 2017 to December 2019 in Balıkesir Atatürk State Hospital were included. Blood cultures were incubated in automated device (Render Biotech Co.Ltd., PRC). Other cultures were incubated with conventional methods. Grown colonies were identified by PhoenixTM 100 automated system (Becton Dickinson, USA). Identifications that need confirmation or strains identified to genus level were further evaluated with conventional techniques. Antimicrobial susceptibility tests were performed by same system, Kirby-Bauer disc diffusion and gradient strip method according to EUCAST guidelines.

Results: 43.1%, 27.1%, 14.7% and 15.1% of enterococci were isolated from urine, blood/sterile body fluids, wound/abscess and other samples. Majority of the strains were ciprofloxacin (72.0%) and levofloxacin (74.1%) resistant, and more than 40% showed ampicillin and high-level gentamicin resistance. Glycopeptide resistance was relatively high (5.4%), especially when considering *E. faecium* (12.1%). There was not any tigecycline and linezolid resistance.

Conclusion: Antimicrobial resistance is a serious and growing public health problem affecting all countries, which is not just a topic of medicine, but multiple sectors such as commercial companies, food industry, veterinarians, etc. High percentages of resistance strongly indicate to get a local action, which should be followed by national and global one.

Keywords: Enterococci, vancomycin, antimicrobial stewardship, EUCAST, CLSI

INTRODUCTION

Enterococci exist in most foods such as raw meat, cheese, milk, and vegetables, since they also play role in fermentation process. Due to their natural habitat, human-enterococci interaction is very tight, and they are significant members of human intestinal microbiota; however they are known to cause both healthcare-associated and community-associated infections in mild to severe spectrum, including urinary tract (UTIs) and bloodstream infections (BSIs) (1,2). *Enterococcus faecalis* and *Enterococcus faecium* are the most common causative agents (>90%) (1).

In recent years, these species also took their place in the antibiotic resistance. The Centers for Disease Control and Prevention (CDC) has declared vancomycin-resistant enterococci (VRE) as a serious threat in 2019, since approximately 30% of all healthcare-associated enterococcal infections show resistance to vancomycin. Although VRE rates are high in healthcare-associated infections, community-associated infections also show such resistance, but in lower rates (3). Especially *E. faecium* has several mechanisms of intrinsic resistance and may show different acquired resistance mechanisms provided by gene mutations or incorporations by plasmids, transpozons, or integrons (4). In addition, despite their infrequent isolation from infection sites, some particular species such as *E. gallinaru*m and *E. casseliflavus* show intrinsic resistance to several antibiotics (5).

Investigation of prevalence on isolated microorganisms from various cultures and antibiotic susceptibilities may give the physicians information about empiric therapies and may provide capability to observe significant changes during the following years. The aim of this study was to investigate the prevalence of *Enterococcus* species and to evaluate susceptibilities to antimicrobial agents in a state (secondary) hospital.

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MATERIAL AND METHOD

Approved by Ethics Committee of Balıkesir University, Faculty of Medicine (Date: 10.06.2020, Decision No: 2020/98). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Cultures obtained from January 2017 to December 2019 in Balıkesir Atatürk State Hospital were included in the study. The three-year period data were evaluated for isolated enterococci and their antimicrobial susceptibilities, retrospectively. A total of 1676 enterococci isolates (490 *E. faecium*, 1146 *E. faecalis*, 10 *E. casseliflavus*/*E. gallinaru*m and 30 other *Enterococcus* species) were included in the study.

The only first sample was included for repetitious samples from the same patient and BSI episodes were determined according to CDC criteria and clinical evaluations (6). BacT/Alert® 3D (bioMérieux, Marcyl'Etoile, France) and Render BC128 (Shandong Huifa Electronics Technology Co., Ltd., PRC) automated blood culture systems were used for blood cultures (BCs) and incubation period was determined according to manufacturer's recommendations. Other cultures were applied and incubated with conventional methods. Grown colonies were identified by PhoenixTM 100 automated system (Becton Dickinson, USA). Identifications that need confirmation or strains identified to genus level were further evaluated with conventional techniques. Contaminations of BCs were determined according to CDC criteria and clinical evaluations (6).

Antimicrobial susceptibility tests were performed by PhoenixTM 100 automated system (Becton Dickinson, USA) and by Kirby-Bauer disc diffusion and gradient strip method according to guidelines of The European Committee on Antimicrobial Susceptibility Testing (EUCAST) (7). Observed vancomycin and teicoplanin resistance and uncertain results (fuzzy zone edges) in disc diffusion were further confirmed with automated system and gradient strip method. Isolates with high-level gentamicin resistance were further tested for high-level streptomycin resistance.

RESULTS

A total of 1676 enterococci isolates were included in the study, and over than 97% of them were the most common causative species; *E. faecalis* (n=1146, 68.4%) and *E. faecium* (n=490, 29.2%). *Enterococcus*-isolated cultures were predominantly from urinary tract samples (n=722, 43.1%), followed by sterile body fluids, including blood (n=455, 27.1%). Since our facility is continuously screened for VRE in specific patients, especially in the ICUs, 72 samples were rectal swabs and 39 isolates (34 *E. faecium*, 5 *E. faecalis*) were detected as vancomycin resistant, which covers approximately a half of such resistant strains. The majority of other VRE were isolated from urinary tract (n=19) and blood (n=12) samples. Despite relatively high resistance rates to quinolones and aminoglycosides, there was no linezolid and tigecycline resistant strain.

All results were presented in **Table 1** and **2**, comparison with The Turkish National Antimicrobial Resistance Surveillance System (UAMDSS) was presented in **Table 3**.

DISCUSSION

Enterococcus, with over than 50 species, are natural inhabitants of humans and animals; however, they remain to be important pathogens of human infections. UTIs, intraabdominal abscesses and BSIs are major manifestations, in addition these species may cause healthcare-associated infections, including biofilm formations on medical devices (8,9).

Enterococci also hold major importance due to several intrinsic resistance and ability to create acquired resistance rapidly. Glycopeptide resistance is the major problem that particularly *E. faecium* strains show this resistance. Since VRE is a public health issue, these strains should be continuously under surveillance of infection control committees (10). Recently, several types of glycopeptide resistance were defined (VanA, B, C, D, E, F, G, L, M, N). Van A and B are the most frequent ones; however, their level of resistance varies (4). VRE strains also show higher resistance rates to other antibiotics, such as gentamicin and

Table 1. Distribution of isolated species according to sample type

Sample / Species	*E. faecium* (n= 490, 29.2%)	*E. faecalis* (n= 1146, 68.4%)	*E. casseliflavus*/ *E. gallinarum* (n= 10, 0.6%)	Other *Enterococcus* spp. (n= 30, 1.8%)	Overall (n,%)	
Blood and Other Sterile Body Fluids	146	292	4	12	454	27.1
Urine	190	517	3	11	721	43.0
Wound/Abscess	57	182	0	7	246	14.7
Respiratory (Upper, Lower) Samples	10	13	0	0	23	1.4
Other (e.g., rectal swab)	87	142	3	0	232	13.7
Total	490	1146	10	30	1676	100

Table 2. Antibiotic resistance profiles of *Enterococcus* species

Antibiotics / Species	*E. faecium* (n= 490, 29.2%)			*E. faecalis* (n= 1146, 68.4%)			*E. casseliflavus/ E. gallinarum* (n= 10, 0.6%)			Other *Enterococcus* spp. (n= 30, 1.8%)			Overall		
	S (n)	R (n)	R-Rate (%)	S (n)	R (n)	R-Rate (%)	S (n)	R (n)	R-Rate (%)	S (n)	R (n)	R-Rate (%)	S (n)	R (n)	R-Rate (%)
Ampicillin[b]	64	379	85.6	921	23[c]	2.4	8	2	20.0	19	7	26.9	1012	411	28.9
Levofloxacin[a]	30	155	83.8	145	353	70.9	2	0	None	1	0	None	178	508	74.1
Ciprofloxacin[a]	31	159	83.7	160	351	68.7	2	0	None	6	1	14.3	199	511	72.0
Teicoplanin	390	54	12.1[c]	927	23	2.4[c]	10	0	None	24	1	4.0	1354	78	5.4
Vancomycin	390	54	12.1[c]	936	23	2.4[c]		NA		24	1	4.0	1350	78	5.4
Linezolid	443	0	None	941	0	None	10	0	None	24	0	None	1418	0	None
Gentamicin (high-level)[1]	284	206	42.0	679	467	40.8	8	2	20.0	19	5	20.8	990	680	40.7
Streptomycin (high-level)[1]	81	338	80.7	508	360	41.5	5	5	50.0	21	9	30.0	615	712	53.7
Tigecycline	95	0	None	740	0	None	5	0	None		ID		840	0	None
Amoxicillin & Clavulanic acid[b]	16	90	84.9	289	12	3.9	1	0	None	11	1	8.3	317	103	24.5
Ampicillin &Sulbactam[b]	4	2	33.3	85	2	2.3	1	0	None	4	1	20.0	94	5	5.1
Nitrofurantoin[a]		NA		496	21	4.1		NA			NA			NA	
Quinupristin-dalfopristin	240	70	22.6		NA			NA			NA			NA	

[a]Uncomplicated UTI only; [b]For UTI or IV administration only; [c]Confirmed with MIC; NA: Not Applicable/Intrinsic Resistance; ID: Insufficient Data
[1]High-level gentamicin resistant strains may not be high-level resistant to streptomycin. Therefore, only strains detected as gentamicin resistant were further evaluated for streptomycin resistance. This selected evaluation resulted with misleading higher levels of streptomycin resistance.

Table 3. Comparison of UAMDSS and present study (17)

Years	Present Studyd	UAMDSS					
		2011[c]	2012[c]	2013[c]	2014[c,d]	2015[c,d]	2016[c,d]
Antibiotics / *E. faecium*				R-Rate (%)			
Ampicillin[a]	85.6	88.1	85.3	100	82.0	87.0	91.6
Teicoplanin[b]	12.1	0.3	16.0	18.4	ID	ID	ID
Vancomycin[b]	12.1	17.0	16.7	22.8	16.0	16.0	16.0
Linezolid	None	0.6	2.7	1.1	4.0	4.0	1.0
Gentamicin (high-level)	42.0	52.3	51.2	43.6	43.0	69.0	61.7
Streptomycin (high-level)	80.7[1]	49.0	36.0	47.3	ID	ID	ID
Antibiotics /*E. faecalis*				R-Rate (%)			
Ampicillin[a]	2.4	9.7	None	4.7	8.0	9.0	6.0
Teicoplanin[b]	2.4	0.3	None	0.2	ID	ID	ID
Vancomycin[b]	2.4	0.9	0.6	0.9	3.0	3.0	1.3
Linezolid	None	0.4	2.0	0.8	3.0	2.0	None
Gentamicin (high-level)	40.8	29.2	31.8	21.4	22.0	54.0	57.2
Streptomycin (high-level)	41.5[1]	31.1	23.3	26.0	ID	ID	ID

[a]For UTI or IV administration only; [b]Confirmed with MIC; [c]CLSI results; d EUCAST results; NA: Not Applicable/Intrinsic Resistance; ID: Insufficient Data; UAMDSS: Turkish National Antimicrobial Resistance Surveillance System
[1]High-level gentamicin resistant strains may not be high-level resistant to streptomycin. Therefore, only strains detected as gentamicin resistant were further evaluated for streptomycin resistance. This selected evaluation resulted with misleading higher levels of streptomycin resistance.

streptomycin (11). Linezolid resistance is another problem, which is claimed to be related to antibiotic exposure such as in staphylococci; however, resistant strains were also detected in cases without any such kind of history (10). In addition, particular species (*E. casseliflavus*/*E. gallinarum*) shows intrinsic resistance to specific antibiotics (5). Interestingly, resistance to a particular antibiotic is not only associated with its usage individually, since cross-resistance depending on the consumption of other antibiotics was also reported (e.g.; cephalosporins and vancomycin) (12).

Several studies focused on the origin and resistance of enterococci. One of the widest studies in European countries is the "The Central Asian and European Surveillance of Antimicrobial Resistance Network (CAESAR)" report, which indicates a serious burden of enterococcal vancomycin resistance especially in the eastern area, including Turkey (VR-*E. faecium* 10-25% interval); furthermore, who declared VR-*E. faecium* as one of the high-priority pathogens that urgently needs new antibiotics for treatment (13,14). Our findings are similar to CAESAR report for both *E. faecium* and *E. faecalis* regarding ampicillin (85.6% & 2.4% vs. 86% &

4%), high-level gentamicin (42% & 40.8% vs. 55% & 37%), vancomycin (12.1% & 2.4% vs. 14% & 1%) and linezolid (None vs. None) resistance. Our higher rates for VR-*E. faecalis* can be explained with the CAESAR sample spectrum, since only cerebrospinal fluid and BC results are included in CAESAR surveillance, but our findings also cover rectal swab screenings. In another study focusing on 10-year BC data in Turkey, while glycopeptide (from 6.2% to 15%) and ampicillin resistance (from 36.7% to 46%) increased, high-level gentamicin resistance dropped (from 66.4% to 39%) for all *Enterococcus* spp. The authors claimed this because of changing prescribing obligations in their facility regarding gentamicin consumption (15). In a wide study in 2016, *Enterococcus* spp. were isolated in 2.9% of 7-years of BCs and ampicillin resistance was 75-100% while vancomycin resistance was even 32.3% in 2010 (2008-2014; 0-32.3%) for *E. faecium* (*E. faecalis*; ampicillin resistance 3.7-16.2%, vancomycin resistance 0-5.9%) (16). In a meta-analysis from Turkey focusing data of 2000-2015; ampicillin, vancomycin, high-level gentamicin, high-level streptomycin, ciprofloxacin, levofloxacin and linezolid resistance of *E. faecalis* was found 24.7±29.4%, 2.2±1.0%, 37.1±17.1%, 43.2±18.3%, 41.0±20.8%, 44.6±20.5% and 1.9±2.6%, respectively, and for *E. faecium*, they were found as 82.5±16.6%, 10.3±11.3%, 58.7±13.4%, 74.4±8.1%, 77.5±17.4%, 21.0% and 2.4%, respectively (1). These high rates of VRE do not reflect a recent problem since Canadian surveillance of CANWARD, CDC, ECDC and WHO has continuously monitored it for several years. For that matter, VRE is among the serious threats in many national surveillance studies. Turkish public health authorities performed UAMDSS project, which showed glycopeptide, aminoglycoside and linezolid resistance of *E. faecium* and *E. faecalis* steadily increased (**Table 3**) (17). Even though the same sample spectrum issue is also valid for UAMDSS, our data seem compatible. Additionally, it is notable that particularly our glycopeptide and fluoroquinolone resistance showed an increasing trend in this three-year period, however statistical analysis was not performed (data not shown).

High-level gentamicin resistant strains may not indicate high-level resistance to streptomycin (5). Therefore, in our study, only strains detected as gentamicin resistant were further evaluated for streptomycin resistance. So, levels of streptomycin resistance (53.7%) seem to be relatively higher than gentamicin resistance (40.7%); however, this situation should be considered in this regard.

The issue in comparison between previous results (e.g., UAMDSS) and this study is the methodological difference. This study is based on EUCAST techniques, while many other studies worldwide, including Turkey, were often based on The Clinical & Laboratory Standards Institute-CLSI. It is possible to observe lower susceptibility results with EUCAST, thus our resistance rates may seem to be slightly higher (18). However, comparison of these two methods is beyond the scope of this study, and both methods actually indicate therapeutic success, so we believe our results will be good local predictors for such information and a good source of data for national surveillance.

Antibiotic consumption has been strongly associated with resistance to such pitch that WHO has been performing surveillance (e.g., European Surveillance of Antimicrobial Consumption-ESAC Project), furthermore CLSI and Turkish Microbiology Society (TMC) endorse laboratories to limit reporting of susceptibility results according to local and/or national antimicrobial stewardship programs (19-21). In the OECD report, Turkey had the highest antibiotic consumption rates in 2015, and despite all efforts, Turkey's statistics on antibiotic consumption shows only limited success. Turkish authorities applied a national action plan regarding drug use for 2014–2017 (22). On the other hand, close monitoring of hospital antibiotic use with local antimicrobial resistance surveillance seems crucial to reflect national policies to hospital level.

CONCLUSION

Antimicrobial resistance is a serious and growing public health problem affecting all countries and multiple sectors. There is an increasing trend of awareness to this issue; however, the fight against it is a multiple-stage approach starting with determining the scope of the problem, which is crucial to monitoring and create an effective response. Standardization and continuousness of antimicrobial susceptibility testing in clinical practice, and accordingly collecting reliable data on antimicrobial resistance are the first stages, which should start from local health facilities.

The data in this study should be interpreted with caution since they may not fully represent the current national status, but they just give clues for results of a comprehensive surveillance system. However, high percentages of resistance strongly indicate the need of a local action, followed by national and global ones. We believe this data will encourage laboratories and clinicians to pay more attention in following and applying national and global antimicrobial stewardship policies.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approved by Ethics Committee of Balıkesir University, Faculty of Medicine (Date: 10.06.2020, Decision No: 2020/98).

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. Kilbas I, Ciftci IH. Antimicrobial resistance of *Enterococcus* isolates in Turkey: A meta-analysis of current studies. J Glob Antimicrob Res 2018; 12: 26-30.
2. Calonico C, Pesavento G, Delfino V, Forni S, Nostro AL. Prevalence of Antibiotic Resistance in Enterococci: A 14 Year Survey. J Food Nutr Res 2018; 6: 626-37.
3. Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019. (doi: 10.15620/cdc:82532)
4. Sieńko A, Czaban S, Ojdana D, et al. Comparison of antibiotic resistance and virulence in vancomycin-susceptible and vancomycin-resistant *Enterococcus faecium* strains. J Med Sci 2018; 87: 195-203.
5. The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Intrinsic resistance and unusual phenotypes version 3.2. Available at https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Expert_Rules/2020/Intrinsic_Resistance_and_Unusual_Phenotypes_Tables_v3.2_20200225.pdf (Date of Access: 31 May 2020).
6. Centers for Disease Control and Prevention (CDC). Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and non-central line-associated Bloodstream Infection). Available at https://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf (Date of Access: 2 Feb 2020).
7. The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters version 11.0. Available at https://www.eucast.org/clinical_breakpoints/ (Date of Access: 16 December 2020).
8. Ahmed MO, Baptiste KE. Vancomycin-resistant enterococci: a review of antimicrobial resistance mechanisms and perspectives of human and animal health. Microb Drug Resist 2018; 24: 590-606.
9. Shridhar S, Dhanashree B. Antibiotic Susceptibility Pattern and Biofilm Formation in Clinical Isolates of *Enterococcus* spp. Interdiscip Perspect Infect Dis 2019. doi: 10.1155/2019/7854968.
10. Miller WR, Murray BE, Rice LB, Arias CA. Vancomycin-Resistant Enterococci: Therapeutic Challenges in the 21st Century. Infect Dis Clin North Am 2016; 30: 35-9.
11. Baldir G, Engin DO, Kucukercan M, et al. High-level resistance to aminoglycoside, vancomycin, and linezolid in Enterococci strains. J Microb Infect Dis 2013; 3: 100-3.
12. Pourmand A, Mazer-Amirshahi M, Jasani G, May L. Emerging trends in antibiotic resistance: implications for emergency medicine. Am J Emerg Med 2017; 35: 1172-6.
13. World Health Organization (WHO). Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR), Annual 2019 Report, 2019. Available at https://www.euro.who.int/__data/assets/pdf_file/0003/418863/53373-WHO-CAESAR-annual-report-2019.pdf (Date of Access: 16 December 2020).
14. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed (Date of Access: 16 December 2020).
15. Mataj V, Guney M, Sig AK, et al. An Investigation into bacterial bloodstream infections and antibiotic resistance profiles in a tertiary hospital for a ten-year period. Clin Lab 2020; 66: 1467-77.
16. Gandra S, Mojica N, Klein EY, et al. Trends in antibiotic resistance among major bacterial pathogens isolated from blood cultures tested at a large private laboratory network in India, 2008–2014. Int J Infect Dis 2016; 50: 75-82.
17. https://hsgm.saglik.gov.tr/tr/uamdss (Date of Access: 16 December 2020).
18. Cusack TP, Ashley EA, Ling CL, et al. Impact of CLSI and EUCAST breakpoint discrepancies on reporting of antimicrobial susceptibility and AMR surveillance. Clin Microb Infect 2019; 25: 910-1.
19. Versporten A, Bolokhovets G, Ghazaryan L, et al. Antibiotic use in Eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. Lancet Infect Dis 2014; 14: 381-7.
20. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; CLSI document M100-30th Edition. Weinstein, MP: Clinical and Laboratory Standards Institute; 2020.
21. https://www.tmc-online.org/userfiles/file/26-37.pdf (Date of Access: 16 December 2020).
22. Isler B, Keske Ş, Aksoy M, et al. Antibiotic overconsumption and resistance in Turkey. Clin Microb Infect 2019; 25: 651-3.

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Head and neck lymphomas from otolaryngology perspective

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ABSTRACT

Aim: To evaluate the clinical manifestations, histopathologic composition, and demographic characteristics of the lymphomas presented in the head and neck.

Material and Method: Records of subjects who had a diagnosis of lymphoma by an otolaryngology clinic in a tertiary referral hospital between May 2007 and July 2017 were reviewed. Demographic features and data regarding histopathology, radiology, and clinical presentation were evaluated.

Results: A total of 103 lymphomas in the head and neck region, 79 (77%) nodal lymphoma, and 24 (23%) extranodal lymphoma, were diagnosed. The initial presentation was solitary lymphadenopathy in 12 (15%) of the nodal lymphomas but conglomerated or multiple lymphadenopathies in the others. No significant relationship was found between lymph node size and histopathology (p=0.144). Extranodal lymphomas presented most commonly in tonsils (n=8, 33%). Hodgkin lymphoma to non-Hodgkin lymphoma ratio was 0.8 (35/44) among nodal lymphomas. The dominant subgroup of non-Hodgkin lymphomas was diffuse large b-cell lymphoma (n=18, 40%). All of the Hodgkin lymphomas in our series were classic variant, and the subjects were younger than the non-Hodgkin lymphomas (z=-4.803, p<0.001). The histopathology of 46 (68%) of non-Hodgkin lymphomas was aggressive. T/NK-cell NHL was detected in seven subjects (6.8%). This was the only group with male predominance (n=5, 71%).

Conclusion: Lymphomas are a large group of malignancies that can present in various clinical forms in the head and neck region. The gender and age of onset of this neoplasm differ by many biological, environmental, and epidemiological factors. Ultrasound findings are crucial in evaluating suspicious lymph nodes. A tissue biopsy is recommended to exclude lymphomas from other neoplasms to make an accurate diagnosis.

Keywords: Lymphoma, head and neck, malignancy

INTRODUCTION

Lymphomas are malignancies originating from the lymphoreticular system. They are the third most common malignancies of the head and neck region after squamous cell cancers and thyroid cancers (1). They should be considered in the differential diagnosis of a patient presenting with a neck mass. But the diagnosis can sometimes be tricky. Although they arise mostly from lymph nodes (NL), they may develop as extranodal lymphoma (ENL) from non-lymph node tissues. According to the histological features, they are divided into two main groups as Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). Besides, NHL is classified into two subgroups as b-cell, and t/NK-cell, depending on the cell type in which it develops. However, a large number of subclasses of all subgroups have been identified. Since clinical behavior and treatment plan is different, it is indispensable to determine the subgroup and subclass correctly. The most comprehensive reference in this field is the World Health Organization (WHO) categorization system, based on pathological, clinical, and genetic factors (2).

There is a need for studies that deal with lymphomas in the head and neck region. Therefore, in this study, head and neck lymphomas, which are frequently encountered in otolaryngology practice, were specifically addressed. The 10-year retrospective records of patients diagnosed with lymphoma by an otolaryngology clinic in a tertiary referral center were reviewed, and demographic characteristics, histopathology, radiology, and clinical presentation were evaluated. The fundamental management strategies that should be applied in a subject with lymphoma or possible

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lymphoma in the head and neck region were discussed in the light of the literature. Consequently, it is aimed to convey the ENT perspective on this issue.

MATERIAL AND METHOD

The study was carried out in full compliance with the Declaration of Helsinki, and the Gazi University Assessment and Evaluation Ethics Sub-Working Group has approved the study (Date: 14.05.2019, Decision No: 91610558-604.01.02-05).

The records of the subjects diagnosed with lymphoma between May 2007 and July 2017 at a tertiary otolaryngology clinic were retrospectively reviewed. Subjects who had a previous diagnosis of lymphoma were excluded. Demographic features and data regarding symptoms, clinical presentation, location of the mass (es), radiological findings, and histopathological type were evaluated.

Lymphomas were classified by reference to the World Health Organization (WHO) system according to their origin and histopathological composition (1). The groups were analyzed comparatively with the demographic characteristics of the patients. The largest diameters of nodal lymphomas and the relationship of lymph node size with histopathology and demographic characteristics were evaluated. Besides, lymphomas were grouped according to their aggressiveness of histopathology, and the relation with other parameters was also evaluated.

Shapiro-Wilk and Kolmogorov-Smirnov tests were used for normality analysis of continuous variables according to the size of the samples and groups. In order to compare the groups, the Mann-WhitneyU test was used for continuous variables, and the $\chi 2$ test was used for categorical variables. IBM Statistical Package for the Social Sciences (SPSS) version 21.0 (Illinois, Chicago) was used for statistical analysis of the data. The results of the study were presented in the light of our clinical practice and literature.

RESULTS

The population consisted of 103 subjects (57 female, 46 male, F/M=1.24). The mean age was 50 years (range 3-85, SD=20.8).

Nodal lymphoma (NL) was detected in 79 (77%) of the subjects, and extranodal lymphoma (ENL) in 24 (23%).

In the NL group, 43 (54%) subjects were female, and the mean age of the whole group was 48 years (range 3-85, SD=21.6).

Among nodal lymphoma subgroups, the mean age of Hodgkin lymphoma (HL) and non-Hodgkin NHL groups were 34 and 59 years, respectively. Subjects with HL in this series were significantly younger than subjects with NHL ($z=-4.803$, $p<0.001$) in the NL subgroup. Both HL and NHL subgroups has a slight female dominance (F/M ratios 1.3 and 1.1, respectively, $p=0.66$).

All of the Hodgkin lymphomas in our series were nodal lymphoma and in classical HL subtype. In 20 (57%) of the subjects mixed cellular type, in 14 (40%) of the subjects nodular sclerosing type, and in one (3%) case lymphocyte-rich type were detected.

The nodal NHL group had a large histopathological composition. The most common was diffuse large b-cell lymphoma (DLBCL) in 18 of the subjects (40%). The other subtypes are listed in **Table 1**.

The subjects diagnosed as NL were evaluated by neck ultrasound (US) and colour doppler ultrasound. The location of the lymph nodes in the neck was the deep jugular chain mostly, and the rarest locations were submental and central compartment (**Table 2**). In 12 (15%) of the subjects, the largest diameter of the most prominent lymph node was less than two centimeters (cm). These lymph nodes were solitary and had suspicious sonographic findings. All the other subjects presented with large, multiple, or conglomerated lymph nodes. No significant relationship was found between lymph node size and histopathology (HL or NHL) ($p=0.144$).

Table 1. Histopatological subtypes of lymphomas

Nodal Lymphoma, n=79		Extranodal Lymphoma, n=24	
Hodgkin, n=35	**Non-Hodgkin, n=44**	**Non-Hodgkin, n=24**	
• Mixt cellular, n=20	• DLBCL, n=18	**b-cell lymphoma, n=22**	**t/NK-Cell lymphoma, n=2**
• Nodular sclerosing, n=14	• Low grade follicular*, n=9	• DLBC, n=12	• Angioimmunoblastic t-cell, n=1
• Lymphocyte rich, n=1	• Marginal zone*, n=5	• Marginal zone*, n=8	• NK-cell, n=1
	• Mantle cell, n=4	• Mantle cell, n=2	
	• Angioimmunoblastic t-cell, n=3		
	• Burkitt, n=2		
	• Peripheric t-cell, n=1		
	• t-cell lymphoblastic, n=1		
	• b-cell lymphoblastic, n=1		

*: Indolent subtypes; NK: Naturale killer; DLBC: Diffuse large b-cell lymphoma

Table 2. Primary localization of Nodal lymphomas	
Lymph node levels	**n (%)**
Zone II	20 (25)
Zone Ib	18 (23)
Zone IV	18 (23)
Zone V	14 (18)
Zone III	6 (7.5)
Zone Ia	2 (2.5)
Zone VI	1 (1)
Total	79 (100)

Seven patients underwent US-guided fine-needle aspiration biopsy (FNAB) prior to excision; atypical lymphoid cells were observed in three of them, and four were reported as non-diagnostic. The definitive diagnosis was made in all patients after diagnostic excision.

The ENL group consisted of 24 subjects. The mean age was 57, and 14 (58%) of the subjects were female. The subjects with ENL were older than the subjects with NL (57 ±16.2 and 48±21.6 respectively, p=0.078). Both groups had a female predominance (p=0.736). ENL developed most commonly from palatine tonsils (n=8, 33%). The other locations are listed in **Table 3**.

Table 3. Primary localization of extranodal lymphomas	
Extranodal region	**n (%)**
Tonsil	8 (33.3)
Nasopharynx	5 (20.8)
Parotid gland	5 (20.8)
Hard palate	2 (8.3)
Gingiva	1 (4.2)
Orbita	1 (4.2)
Lower lip	1 (4.2)
Trachea	1 (4.2)
Total	24 (100)

Twenty-two subjects (91%) with ENL had b-cell NHL, and only two (9%) had t/NK-cell lymphoma. The most common histopathologic subtypes were DLBCL (41%, n=9) and marginal zone b-cell lymphoma (36%, n=8).

Among all subjects, a sum of seven patients (6.8%) was diagnosed as t/NK-cell NHL. This was the only group with male predominance (n=5, 71%). The mean age in this group was 41 and significantly younger than b-cell NHL (mean age=60, n=61) (p=0.004). The nodal onset rate was 71% (n=5) in t/NK cell lymphomas and was similar to the b-cell lymphomas.

NHL has histopathologically aggressive and indolent types. In our series, 46 (68%) had aggressive histopathology. There was no significant difference between aggressive and indolent NHL in terms of gender (p=0.291).

DISCUSSION

Lymphomas are malignant neoplastic proliferation of the lymphoreticular system. They often arise from lymph nodes, but they can develop from any tissue with lymph flow. Enlarged, painless lymphadenopathy (LAP) is mostly the main clinical symptom. On physical examination, enlarged nodes in lymphoma are rubbery and mobile (3). Approximately 80% of HL and 10-20% of NHL cases manifest as an enlarged lymph node within the head and neck region (4). In 20-30% of these subjects, lymphomas derive from extranodal tissues (5). In our study, 24% of the lymphomas derived from extranodal tissues, which is similar to the literature.

In previous studies, the most common ENL origins were reported as the Waldeyer's ring (6) or the sinonasal region (7,8). In our study, the most common location of masses related to NHL was palatine tonsil (33%), followed by nasopharynx, parotid gland, and hard palate (**Table 3**). Bilateral tonsillar involvement was seen in one subject and, in all other cases, presented with unilateral tonsil hypertrophy. Diagnostic tonsillectomy should be considered particularly in unilateral tonsillar hypertropy (8). Sinonasal NHL has been reported more in Asian countries than in western countries (9). However, ENL can develop from many other tissues in the head and neck. Because they can mimic squamous cell cancers of the head and neck, a deep tissue biopsy should be performed and confirmed for a definite diagnosis before any radical surgery (3).

Nodal lymphomas often present with large, multiple, and conglomerated lymphadenopathy. There is no difficulty in this group about decision making for diagnostic excision. On the other hand, 15% of the subjects with NL present with small solitary lymph nodes less than two centimeter in the largest diameter. In these subjects, the clinical findings may be masked and suspicious nodes can be overlooked on physical examination. The pathological indicators on ultrasound (US) and colour Doppler US (e.g., spherical lymph nodes with a diameter > 5mm, loss of hilar architecture, presence of intranodal necrosis and calcification, matting, increased hilar and peripheral vascularization) should suggest lymphoma and require excision of the lymph node for further evaluation (10).

Fine needle aspiration biopsy (FNAB) may provide limited data in the differential diagnosis and remains inadequate in most of the situations (11). In our study, FNAB was performed in seven of the subjects presented with small suspicious lymph nodes, but atypical lymphoid cells were detected in only three of them. In the other four, results of the cytological examination were non-diagnostic. A definitive diagnosis was made by excisional lymph node biopsy in all seven cases. Although there

have been reports suggesting tissue diagnosis by core biopsy in recent years, the lymph node excision remains the gold standard in lymphoma (12-14).

Lymph nodes related to NL were rarely encountered in the midline lymph node groups such as level Ia and VI. Only three of the subjects in our series developed LN from the central neck zones. This is probably related to a lower number of total lymph nodes located within these zones compared to the others.

The relationship between lymphoma and gender is heterogeneous in the previous studies (15). This difference should be evaluated with various genetic, social, and environmental characteristics (6,15,16). The exact correlation between the frequency of lymphoma and gender has not been shown. In our study, a slight female predominance was present, but the only exception was t/NK-cell NHL, which was more common in males.

Age distribution of lymphoma varies according to geographical regions. In general, studies published from the western countries have higher mean ages, while the reports from Asian countries have reported earlier mean ages (7,16). In our series, the mean age in the NL and ENL groups was 48 and 57, respectively (p=0.078). The mean age of the HL group in our series was 34, the youngest in our study, and younger than nodal NHL (p=0.141). The incidence of HL increase in the third decade continues to decrease in the following years, but usually increases again after 45 and makes a bimodal peak (17). In our study, only a single peak was detected in the third decade (**Figure**). In addition, the mean age of t/NK-cell NHL was significantly lower than the b-cell NHL. In contrast to our series, t/NK-cell lymphomas reported older (around the age of 60) in large cohorts from the United States. The age of onset of this rare neoplasm is associated with many biological, environmental, and epidemiological factors (18).

Unlike developed countries where the nodular sclerosing type HL is predominant, the mixed cellular type was more common in our study, which is similar to the reports from other developing countries. Mixed cellular type is known as a more aggressive subtype than nodular sclerosing type (19). Viral agents (e.g., Epstein-Barr virus) are blamed for the aetiology of mixed cellular type, and its higher incidence in undeveloped or developing countries may be due to the higher contamination rates (20). All HLs were nodal in our series, and extranodal HL was not detected, which is comparable with previous reports (3).

The most common histopathological type of all cases in our study (both NL and ENL) was NHL, and the most common subgroup was DLBCL. NHL is reviewed in two forms as rapid proliferating (aggressive) and slow-acting (indolent) lymphomas. DLBCL, Burkitt lymphoma, mantle cell lymphoma, most peripheric t-cell lymphomas, both t-cell and b-cell lymphoblastic lymphomas, human immunodeficiency virus (HIV) related lymphomas and transformed lymphomas have aggressive behavior (21). Indolent lymphomas are low-grade follicular lymphoma, marginal zone lymphoma, plasmacytoma, and low-grade b-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (22). Several NHL subtypes are classified as aggressive. In accordance with the literature, aggressive histopathology was found to be 68% predominant in our study (23).

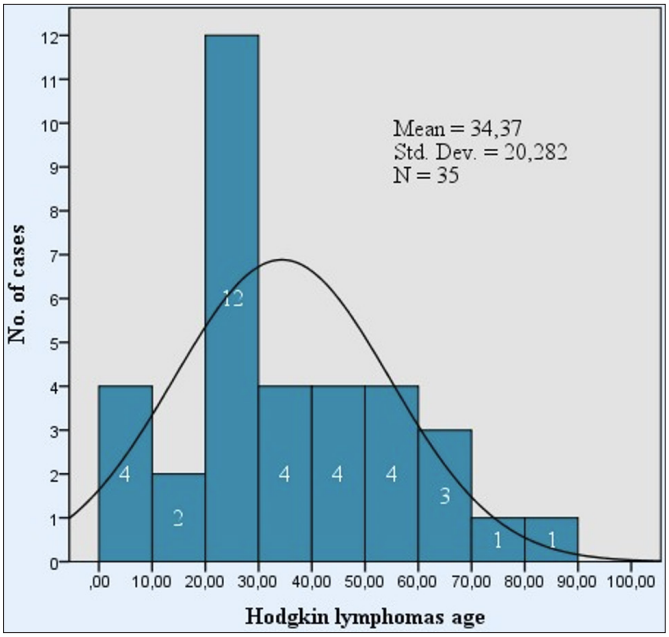

Figure. Histogram demonstrating a single peak in the third decade of the hodgkin lymphoma group.

CONCLUSION

Lymphomas are a large group of malignancies that can present in various clinical forms in the head and neck region. Lymph nodes may not always enlarge in lymphoma. However, conglomerated lymphadenopathy may not always be present. According to our results, 15% of nodal lymphomas present with a solitary lymph node small than two centimeters in the largest dimension. The US has a crucial role to evaluate the lymph nodes in such cases.

NHLs can develop from multifarious extranodal tissues of the head and neck and can mimic other common head and neck malignancies like squamous cell carcinomas. In this respect, it should be considered in the differential diagnosis of head and neck tumors. A tissue biopsy is recommended to exclude lymphomas, and other neoplasms to avoid unnecessary surgeries in such situations.

ETHICAL DECLARATIONS

Ethics Committee Approval: Gazi University Assessment and Evaluation Ethics Sub-Working Group has approved the study (Date: 14.05.2019, Decision No: 91610558-604.01.02-05).

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.

REFERENCES

1. Cooper JS, Porter K, Mallin K, et al. National Cancer Database report on cancer of the head and neck: 10-year update. Head Neck 2009; 31: 748-58.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127: 2375-90.
3. Zapater E, Bagán J, Carbonell F, Basterra J. Malignant lymphoma of the head and neck. Oral Dis 2010; 16: 119-28.
4. Weber AL, Rahemtullah A, Ferry JA. Hodgkin and non-Hodgkin lymphoma of the head and neck: clinical, pathologic, and imaging evaluation. Neuroimaging Clin N Am 2003; 13: 371-92.
5. Urquhart A, Berg R. Hodgkin's and non-Hodgkin's lymphoma of the head and neck. Laryngoscope 2001; 111: 1565-9.
6. Beasley M. Lymphoma of the thyroid and head and neck. Clin Oncol 2012; 24: 345-51.
7. Hanna E, Wanamaker J, Adelstein D, Tubbs R, Lavertu P. Extranodal lymphomas of the head and neck: a 20-year experience. Arch Otolaryngol Head Neck Surg 1997; 123: 1318-23.
8. Oluwasanmi AF, Wood SJ, Baldwin DL, Sipaul F. Malignancy in asymmetrical but otherwise normal palatine tonsils. Ear Nose Throat J 2006; 85: 661-3.
9. Woo J-S, Kim JM, Lee S, Chae S, Hwang S, Lee HM. Clinical analysis of extranodal non-Hodgkin's lymphoma in the sinonasal tract. Eur ArchOtorhinolaryngol 2004; 261: 197-201.
10. Ahuja AT, Ying M, Ho SY, et al. Ultrasound of malignant cervical lymph nodes. Cancer Imaging 2008; 8: 48-56.
11. Burke C, Thomas R, Inglis C, et al. Ultrasound-guided core biopsy in the diagnosis of lymphoma of the head and neck. A 9 year experience. Brit J Radiol 2011; 84: 727-32.
12. Nyquist GG, Tom WD, Mui S. Automatic core needle biopsy: a diagnostic option for head and neck masses. Arch Otolaryngol Head Neck Surg 2008; 134: 184-9.
13. Allin D, David S, Jacob A, Mir N, Giles A, Gibbins N. Use of core biopsy in diagnosing cervical lymphadenopathy: a viable alternative to surgical excisional biopsy of lymph nodes? Ann R Coll Surg Eng 2017; 99: 242-4.
14. Houcine Y, Romdhane E, Blel A, et al. Evaluation of fine needle aspiration cytology in the diagnosis of cervical lymph node lymphomas. J Craniomaxillofac Surg 2018; 46: 1117-20.
15. Etemad-Moghadam S, Tirgary F, Keshavarz S, Alaeddini M. Head and neck non-Hodgkin's lymphoma: a 20-year demographic study of 381 cases. Int J Oral Max Surg 2010; 39: 869-72.
16. Roman E, Smith A. Epidemiology of lymphomas. Histopathology 2011; 58: 4-14.
17. Alexander FE, Ricketts TJ, McKinney PA, Cartwright RA. Community lifestyle characteristics and incidence of Hodgkin's disease in young people. Int J Cancer 1991; 48: 10-4.
18. Phan A, Veldman R, Lechowicz MJ. T-cell lymphoma epidemiology: the known and unknown. Curr Hematol Malig Rep 2016; 11: 492-503.
19. Agostinelli C, Pileri S. Pathobiology of hodgkin lymphoma. Mediterr J Hematol I 2014; 6: e2014040.
20. Glaser SL, Lin RJ, Stewart SL, et al. Epstein-Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. Int J Cancer 1997; 70: 375-82.
21. Said JW. Aggressive B-cell lymphomas: how many categories do we need? Mod Pathol 2013; 26: S42-S56.
22. Fisher RI, Dahlberg S, Nathwani BN, Banks PM, Miller TP, Grogan TM. A clinical analysis of two indolent lymphoma entities: mantle cell lymphoma and marginal zone lymphoma (including the mucosa-associated lymphoid tissue and monocytoid B-cell subcategories): a Southwest Oncology Group study. Blood 1995; 85: 1075-82.
23. Al-Hamadani M, Habermann TM, Cerhan JR, Macon WR, Maurer MJ, Go RS. Non-H odgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol 2015; 90: 790-5.

Original Article

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Does fine needle aspiration from a different nodule other than the dominant nodule provide additional benefit in thyroid diseases with nodules?

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ABSTRACT

Objectives: The incidence of thyroid nodules has increased significantly and malignancy detected in 5-15% of them. While biopsy is recommended for all nodules larger than 1 cm in multinodular goiter, this is practically not possible in many patients. In addition, the relationship between nodule size and malignancy is not clear. We aimed to examine the value of additional biopsy from a nondominant nodule in terms of changing treatment and follow-up decisions and the relationship between nodule size and malignancy risk.

Material and Method: Patients (n=2.541) with thyroid nodules who applied to our clinic for various indications and performed fine needle aspiration between January 1, 2016 and March 1, 2021 were included in the study. Some of our patients with multinodular goiter were biopsied from a second additional nodule. Cytologic evaluations reported according to the Bethesda system. Pathology reports of the operated patients were scanned retrospectivelly.

Results: Fine needle aspiration biopsy was performed from a total of 3382 nodules of 2541 patients. The average age of our patient group was 56 (46-65) and 79% of them were women. When a comparison was made between nodule size and malignancy rate; the highest malignancy rate was detected in nodules between 1-2 cm (61.8%). Finally a diagnosis of Bethesda-4,-5,-6 was reached in only 7 (0.9%) of 823 patients who underwent additional biopsy from nondominant nodule.

Conclusion: The value of an additional biopsy from a second nodule in terms of changing follow-up is very low and not significant and most of the cancers arise from nodules between 1-2 cm. According to our study, the assumptions that the malignancy risk increases as the nodule size or nodule count increase were not found to be correct.

Keywords: Thyroid nodule, fine needle aspiration biopsy, thyroid cancer

INTRODUCTION

Nodularity in thyroid is increasingly detected because of incidental detection on various imaging procedures and increased rate of neck ultrasonography due to thyroid diseases. While the frequency of palpable thyroid nodules is between 4-7% with the use of high resolution ultrasonography, this rate has increased to around 19-67%. Prevalence increases with age and 3-4 times more in women (1-3). Clinically, the most important aspect of thyroid nodules is that 5-15% of them are found to be malignant. According to the literature cancer risk of palpable and nonpalpable nodules are similar (1-3). Thyroid cancer is the most common cancer among endocrine cancers and constitutes 1% of all malignant neoplasms (4,5). Ultrasound-guided fine needle aspiration biopsy (FNAB) has become the gold standard method for the evaluation of thyroid nodules (1,2).

According to a large meta-analysis published in 2013, multinodular goiter (MNG) is reported to be less malignant than solitary nodules especially in iodine-deficient areas (6). Currently similar malignancy rates are given in solitary thyroid nodule and multinodular goiter in the literature (7-9). The average malignancy rate for MNG is defined as 15% (between 4-36%), and around 10-21% for solitary nodule (10,11). Biopsy recommended only from the dominant nodule in some studies, while in others it is emphasized that biopsy should be performed from every nodules that exceed 1 cm or with suspicius ultrasound features (7).

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According to the current ATA (American Thyroid Association) and AACE (American Association of Clinical Endocrinology) guidelines, biopsy from all nodules exceeding 1 cm and/or with suspicious US features, and if this is not possible, biopsy from the dominant nodule of coelescent nodules with the same ultrasonographic features is recommended (12,13).

It has not been clarified yet biopsy of the nondominant nodules will affect the treatment and follow-up decision in MNG. In addition, it is not clear whether the risk of malignancy increases with the increased nodule size. We aimed to find out the answer of these two questions in our study.

MATERIAL AND METHOD

Ethical approval was obtained from the Sakarya University Faculty of Medicine Non-interventional Clinical Researchs Ethics Committee (Date: 11.05.2021, Decision No: E-71522473-050.01.04-32204-321). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients older than 18 who had diagnosed or suspected various thyroid diseases and underwent FNAB from one or more nodules between January 1, 2016 and March 1, 2021 were included in the study. Children, pregnant women, patients with a history of radiation exposure to the neck region, and with familial thyroid cancer history, and patients with a current diagnosis of thyroid cancer were excluded. Serum free T3, free T4, TSH (Thyroid Stimulating Hormone) levels were measured by the chemiluminescent microparticle immunological method in the Abbott Architect I 2000 SR® device. Thyroid and neck ultrasonographies (US) were performed by Endocrinology and Metabolism Physicians with a B Mode High Resolution USG device (Logic 9, General Electric USA®) with a 13 mHz linear probe. In the ultrasonographic evaluation; size of the thyroid tissue in all three planes, echogenicity, doppler blood supply, the detailed location of the nodules their diameters, borders, echogenicity and ultrasonographic features (cystic content, spongioform appearance, microcalcification, macrocalcification foci, etc.) and doppler blood supply charasteristics were specified.

Thyroid scintigraphy was performed before FNAB in patients whom TSH values were at the lower limit of normal and low. The procedure was done with a gamma camera connected to a pinhole collimator.Twenty minutes after intravenous injection of 5 mci Tc99m-pertechnetate, anteroposterior and oblique images were taken and thyroid tissue activity and Tc99m uptake and nodule activities were determined and interpreted by Nuclear Medicine Physicians.

Ultrasound guided FNAB was performed by experienced Endocrinology and Metabolism Physicians on medically indicated patients. The patients were informed in detail about the procedure and their written consents were obtained. The procedure was performed under sterile conditions with a 10 ml syringe combined with a 23 gauge needle without local anesthesia. The target nodule was reached under US and then multiple multidirectional passages were made by applying negative pressure. The process was terminated by taking enough material into the syringe. The samples taken were placed in liquid-based cytology tubes containing 95% ethanol and sent to pathology. The patients generally well-tolerated the procedure and there were no major complications. Tissue materials were examined by experienced pathologists and reported according to the Bethesda system (14).

Surgical operations were performed by general surgeons or otolaryngologists. Lobectomy+isthmectomy or near total or total thyroidectomy procedures were applied to the patients in accordance with their disease. Tissue materials were examined by experienced pathologists.

Laboratory, ultrasonographic data and cytology and pathology reports of the patients were retrospectively scanned from the hospitals online database system. The locations of dominant and nondominant second nodules, which were biopsied, Bethestda classifications, and tissue diagnoses were verified. Biopsied and excised nodules were matched as accurately as possible with the ultrasonographic data.

Statistical analyses were performed by using SPSS version 22 software. The suitability of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov). Categorical variables were described as frequencies and percentages. According to the results of these analyzes, the variables of age, TSH, and FT4 levels were not normally distributed. Descriptive analyses were performed using the median and interquartile range (using frequency tables for ordinal variables) for non-normally distributed variables.

RESULTS

Two thousand five hundred forty one patients with biopsied 3382 nodüles were included in the study. The median age (IQR) value of the patients was 56 (46-65) and the female/male ratio was 2007/534 (79.0%/21.0%). TSH (for n=1423) and fT4 (for n=1367) median (IQR) values were 0.65 mIU/L (0.23-1.45) and 12.2 pmol/L (11.2-13.4), respectively. The clinical characteristics and laboratory findings of the patients and the

characteristics of the nodules are summarized in **Table 1**. According to TSH levels (for n=1,423), 596 (41.9%) patients were hyperthyroid, 32 were hypothyroid (2.2%) and 795 (55.9%) were euthyroid. Fine needle aspiration was performed from at least one nodule of 2541 patients. According to the cytologic evaluation; 588 (23.1%) nodules were category-1, 1608 (63.3%) were category-2, 272 (10.7%) were category-3, 19 (0.7%) were category-4, 39 (1.5%) were category-5 and 15 (0.6%) were in category-6.

Table 1. Baseline characteristics, features of nodules and tissue diagnosis

	Results
Age, years	56 (45-65)
TSH, mIU/L	0.65 (0.23-1.45)
Gender, n (%)	
Female	2007 (79.0)
Male	534 (21.0)
First nodüle, n (%)	2541 (100)
Maximum diameter (mm)	15.0 (10.0-20.0)
min-max	3-70
Location, n (%)	
Right	1208 (47.5)
Left	1136 (44.7)
Isthmus	197 (7.8)
Second (another) nodüle, n (%)	841 (100)
Maximum diameter (mm)	15.0 (10.0-20.0)
min-max	5-60
Location, n (%)	
Right	386 (45.9)
Left	363 (43.2)
Isthmus	92 (10.9)
Tissue diagnosis, n (%)	230 (100)
Benign	154 (67.0)
Papillary thyroid cancer	66 (28.7)
Follicular thyroid cancer	3 (1.3)
NIFTP	4 (1.7)
vWDT-UMP	2 (0.9)
Anaplastic carcinoma	1 (0.4)

Abbreviations: NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; WDT-UMP, well differentiated thyroid tumor of uncertain malignant potential.

Surgery was decided in 73 (2,9%) of 2541 patients because of one or two nodules cytologic evaluation were compatible with Bethesda categories-4,5 and 6. The remaining 2,468 patients were decided for follow-up or re-biopsy because the result was category-1,2, and 3. In 823 patients FNAB was performed from different nodules at different times. Cytologic result of 816 (99.1%) of them were evaluated as compatible with Bethesda category-1,2, and 3, only 7 (0.9) of them were compatible with categories 4,5 and 6 and referred to surgery (**Figure 1**). Eighty-eight (5.5%) of the patients whom FNAB result were compatible with category-2 (benign) were operated for different reasons. Pathological evaluation of 11 (12.5%) of these 88 operated patients was compatible with malignancy (**Figure 2**).

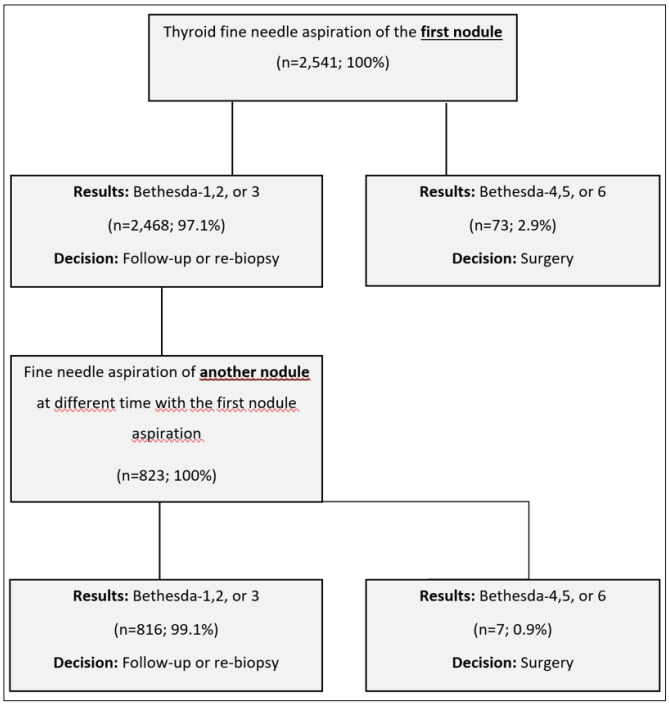

Figure 1. Diagram showing results of thyroid fine needle aspiration

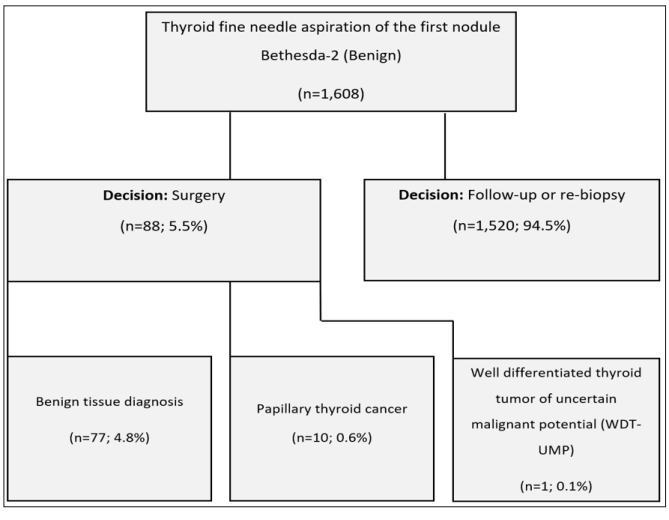

Figure 2. Diagram showing results of thyroid fine needle aspiration

The median (IQR) value of 76 patients who were operated and whose pathology was malignant was 47 (35-55.8) and the majority were women (n=57, 75%). When analyzed according to nodule size, the tumor was mostly in the group with 10-10.9 mm (n=47, 61.8%) (**Table 2**).

Table 2. Clinical features of operated patients with malign pathology

	Results (n=76)
Age, years	47.0 (39.0-55.8)
Gender, n (%)	
Female	57 (75.0)
Male	19 (25.0)
Nodule size (maximum diameter), mm	
<10	8 (10.5)
10-10.9	47 (61.8)
20-39.9	16 (21.1)
≥40	5 (6.6)
Nodule location, n (%)	
Right lobe	34 (44.7)
Left lobe	31 (40.8)
Isthmus	11 (14.5)

DISCUSSION

High-resolution ultrasonography is now widely used in our country and nodule biopsy is almost completely performed by US. Therefore the rate of detecting thyroid nodules and the accuracy of FNAB is increasing.

The average age of our patient group was 56 (45-65) and 79% of them were women. The mean age of cancer group was found to be 47 (39-55.8) and 75% of them were female. The average age of our nodule and cancer patients is consistent with the literature (4,10,11,15). Of the 76 patients with malignancy, 66 (86%) were papillary thyroid carcinoma, 3 (3.9%) were follicular thyroid carcinoma, and these rates are also consistent with the literature (4,7,10,16).

According to the guidelines; the malignancy rate of all palpable and nonpalpable nodules were assumed to be equal and recommended biopsy from all nodules above 1 cm; If this is not possible, biopsy is recommended from the largest one of the coelescent nodules with the same character (dominant nodule) or the nodule with suspicius ultrasonographic findings (12,13). However the probability of malignancy in MNG was generally found to be equal to or lower than solitary nodüle in the literature (6-10). In clinical practice, performing multiple biopsy from a patient from many nodules is more difficult to tolerate, time-consuming and costly (7). Therefore, we wondered how valuable the multiple nodule biopsy procedure is in terms of patient follow-up and in making the surgical decision. According to our data, only 7 of the 823 patients was malignant who had a second nodule biopsy; this led to an additional surgery decision of 0.9% according to the total number of patients. In other words, we found that biopsy from an additional nodule detected malignancy in very few patients and changed the treatment decision.

When studies that performed nodule biopsies from nondominant nodules in MNG were examined, in the study of Frates et al. (7) 3483 nodules of 1985 patients were biopsied. According to this study, in patients with multiple nodules larger than 10 mm, 72% of cancers were detected in the largest nodule, and 46% were multifocal. According to the results of the same study, the strategy of taking the largest nodule biopsy could detect only 86% of patients with cancer with two nodules, whereas approximately 50% of patients with cancer with three or more nodules. In the study of Paksoy et al. (11) 35.7% of the detected malignancies were found in the nondominant nodule and multiple nodule biopsy, preferably from different lobes, was recommended. Arısoy et al. (16) was detected 65.5% of a single 34.5% multifocal cancer in 142 patients, and the cure rate of surgery performed only on the dominant nodule side remained at 65%. In another study, cancer was detected with a rate of 14.3% and half of the cancer cases detected in nondominant nodules (17). Surgically confirmed 365 cases were examined in the study by Erbil et al. (18) and 59% of the patients were found to have cancer outside the dominant nodule.

According to the results of these studies; we see that biopsy of one or more nodules other than the dominant nodule in MNG changes the diagnosis and treatment decision significantly. In our study the reason that biopsy from the second nodule was not found very effective in the treatment decision may be the second biopsy was performed on nondominant nodules with the same characteristics as the initial nodules and we did not perform additional biopsy in all patients with MNG.

Sensitivity of fine-needle aspiration biopsy in general ranges between 65-98% and specificity between 72-100% (1,10). In our study, we performed biopsies on a total of 3382 nodules of 2541 patients, 23.1% of these patients were found to be nondiagnostic. The nondiagnostic rates in the literature are between 10-28.2% and our series is compatible with the literature (19). Additionally 88 patients with benign FNAB (Bethesda category 2) underwent surgery for different reasons and malignancy was detected in 11 (12.6%) of them. According to the literature, false negativity rate of FNAB is generally between 1-10%, but in the study of Arısoy et al. this rate rises up to 17% (3,16). The reason for the false negativity rate being slightly higher than the literature in our study may be that all biopsied patients were not undergoing surgery and it was not clarified whether all of the malignancies arised from the nodules that we performed biopsy.

Currently surgery is recommended for nodules above 4 cm, even if the nodule is benign. The high rate of false negativity in FNAB in these nodules supports this recommendation (4,18). It is also a matter of curiosity

whether the size of the nodule affects the possibility of malignancy. In our study, most of the malignancies were detected in nodules between 1 and 2 cm (61,8%), while this rate remained at 10.5% in subscentimetric nodules and 6,6% in above 4 cm nodules. According to a systematic meta-analysis, an increase in the risk of malignancy above 2 cm has been reported (20). Polyzos et al. (21) was found An increased risk in nodules larger than 4 cm. Kamran et al. (22) was found a slightly increased risk of malignancy in nodules larger than 2 cm (<2 cm 10.5% vs > 2 cm 15%). In the studies of Shrestha (7) and Frates et al. (23) no significant difference was found in malignancy rates according to the size of the nodule. On the other hand Cavallo et al. (4) was found significantly increased malignancy rates in nodules smaller than 2 cm and Er et al. (5) found increased malignancy rate of less than 1 cm. When our results are evaluated together with the results of other similar designed studies, it shows that nodule size does not play a very significant role according to the risk of malignancy.

Our study is a single center study designed retrospectively. We could not clarify in a few patients whether the nodules that were biopsied and were found to be malignant during surgery are the same nodules. Fortyone percent of our patient group consists of hyperthyroidic patients. Although there are publications in the literature that hyperactive nodules have a similar malignancy risk with normoactive and hypoactive nodules (24), according to current guidelines, biopsy is not recommended because it is known that the possibility of malignancy in hyperactive nodules is very low (2,3,11,12). We performed Tc99m scintigraphy in hyperthyroidic patients for avoiding biopsy from autonomic nodules, however there is still the possibility of being hyperactive nodules among the nodules we biopsied and therefore the rate of additional malignancy detected in the second nodule may found to be low.

CONCLUSION

The relationship between nodule size and malignancy risk was examined in our study, and the highest rate of malignancy was found in nodules between 1-2 cm. In addition the value of additional biopsy performed from a second nodule in multinodular goiter was found to be very low in terms of changing follow-up and deciding surgery. Although it is a single center study we presented our study with a considerable number of cases and power. We found nondiagnostic and false negativity rates in accordance with the literature and well documented the biopsy and surgical data. We think that the net results of our study will contribute to the literature. Multi-center, large randomized controlled studies are needed to achieve clearer results.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Sakarya University Faculty of Medicine Non-interventional Clinical Researchs Ethics Committee (Date: 11.05.2021, Decision No: E-71522473-050.01.04-32204-321).

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. Ross DS,Cooper DS, Mulder JE, et al. Overview of Thyroid Nodule Formation. UpToDate Clinical Review. Online Available at http://www.uptodate.com Searched at May 2021.
2. Ross DS,Cooper DS, Mulder JE, et al. Diagnostic Approach to and Treatment of Thyroid Nodules. UpToDate Clinical Review. Online Available at http://www.uptodate.com Searched at May 2021.
3. Burman KD, Wartofsky L. Clinical practice thyroid nodules. N Engl J Med 2015; 10: 2347-56.
4. Cavallo A, Johnson DN, White MG, et al. Thyroid nodule size at ultrasound as a predictor of malignancy and final pathologic size. Thyroid 2017; 27: 641-50.
5. Er S, Akın T, Baba S, et al. Relationship between Thyroid Nodule Diameter and Malignancy: Nodüle Diameter Actually Increase Probability of Malignancy? Akd Med J 2017; 3: 191-6.
6. Brito JP, Yarur AJ, Prokop LJ, McIver B, Murad MH, Montori VM. Prevalence of thyroid cancer in multinodular goiter versus single nodule: a systematic review and meta-analysis. Thyroid 2013; 23: 449-55.
7. Frates MC, Benson CB, Doubilet PM, et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metab 2006; 91: 3411-7.
8. Lin YS, Wu HY, Yu MC, Hsu CC, Chao TC. Patient outcomes following surgical management of multinodular goiter: Does multinodularity increase the risk of thyroid malignancy? Medicine (Baltimore) 2016; 95: e4194.
9. Sachmechi I, Miller E, Varatharajah R, et al. Thyroid carcinoma in single cold nodules and in cold nodules of multinodular goiters. Endocr Pract 2000; 6: 5-7.
10. Keh SM, El-Shunnar SK, Palmer T, Ahsan SF. Incidence of malignancy in solitary thyroid nodules. J Laryngol Otol 2015; 129: 677-81.
11. Paksoy N, Yazal K, Corak S. Malignancy rate in nondominant nodules in patients with multinodular goiter: Experience with 1,606 cases evaluated by ultrasound-guided fine needle aspiration cytology. Cytojournal 2011; 8: 19-28.

12. Haugen BR, Alexander EK, Bible KC, et al. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.
13. Gharib H, Papini E, Garber JR, et al. American association of clinical endocrinologists, american college of endocrinology, and associazione medici endocrinology medical guıdelines for clinical practice for the diagnosis and management of thyroid nodules 2016 Update. AACE/ACE/AME task force on thyroid nodules. Endocr Pract 2016; 22: 622-39.
14. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017; 27:1341–6.
15. Erdem H, Yıldırım Ü, Özaydın İ, et al. Retrospective comparison of histopathologic results of thyroid fine-needle aspiration biopsies. Konuralp Tıp Derg 2012; 4: 26-30.
16. Arısoy K, Köksoy FN, Gönüllü D, Ayyıldız İğdem A, Kuru B. The relationship of thyroid cancer with dominant nodule in patients with nodular goiter who underwent total thyroidectomy and had thyroid carcinoma. Ulusal Cerrahi Derg 2012; 28: 182-85.
17. Yong JS, Loh KS, Petersson BF, Thong M. Multinodular goiter: A study of malignancy risk in nondominant nodules. Ear Nose Throat J 2017; 96: 336-42.
18. Erbil Y, Barbaros U, Salmaslioglu A, et al. Effect of thyroid gland volume in preoperative detection of suspected malignant thyroid nodules in a multinodular goiter. Arch Surg 2008; 143: 558-63.
19. Mehanna R, Murphy M, McCarthy J, et al. False negatives in thyroid cytology: impact of large nodule size and follicular variant of papillary carcinoma. Laryngoscope 2013; 123: 1305–09.
20. Shin JJ, Caragacianu D, Randolph GW. Impact of thyroid nodule size on prevalence and post-test probability of malignancy: a systematic review. Laryngoscope 2015; 125: 263-72.
21. Polyzos SA, Kita M, Efstathiadou Z, et al. The use of demographic, ultrasonographic and scintigraphic data in the diagnostic approach of thyroid nodules. Exp Clin Endocrinol Diabetes 2009; 117: 159–64.
22. Kamran SC, Marqusee E, Kim MI, et al. Thyroid nodule size and prediction of cancer. J Clin Endocrinol Metab 2013; 98: 564–70.
23. Shrestha M, Crothers BA, Burch HB. The impact of thyroid nodule size on the risk of malignancy and accuracy of fine-needle aspiration: a 10-year study from a single institution. Thyroid 2012; 22: 1251–6.
24. Baser H, Topaloglu O, Bilginer MC, et al. Are cytologic and histopathologic features of hot thyroid nodules different from cold thyroid nodules? Diagn Cytopathol 2019; 47: 898-903.

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CRP, WBC and monocyte/lymphocyte ratio relation as a preoperative predictive factor for adhesions observed during laparoscopic cholecystectomy

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ABSTRACT

Aim: The purpose of this study to predict adhesion related technical difficulties during operation by comparing preoperative CRP, WBC, Monocyte/Lymphocyte ratio (Mo/Ly) and intra-operative adhesion findings.

Material and Method: This was a retrospective study. This study includes 116 elective and emergency cholelithiasis cases whose operation performed at Çorum Erol Olçok Training and Research Hospital in 2020 and 2021. Adhesions on gallbladder were graded during operation and divided into two groups. Groups graded based on intra-operative findings were compared with preoperative CRP, WBC, and monocyte/lymphocyte ratio.

Results: The patients were divided into two groups based on the adhesion grade as Grade 1-2 (n=84) and Grade 3-4 (n=32). Mean WBC count of Grade 3-4 group was mean 11.05±4.45 10^9/L and this value was statistically significantly higher (p=0.01) than Grade 1-2 group. Mean CRP value of Grade 3-4 group was found as 50.91±77.25 mg/L and this value was significantly elevated (p<0.001) when compared with Grade 1-2 group. Mean monocyte/lymphocyte ratio was found as 0.29±0.18 and 0.52±0.33 for Grade 1-2 and Grade 3-4 groups, respectively and these values were found statistically significant (p<0.001). Adhesions were significantly higher for CRP (>24.5 mg/l), WBC (>11.55 10^9/L), monocyte/lymphocyte ratio (>0.2693) cut-off values.

Conclusion: Preoperative estimation of adhesion grade helps the surgeon considerably. This study shows that high CRP, WBC, and Mo/Ly ratio values can help the estimation of intensity of adhesions and challenges during operation.

Keywords: Cholecystectomy, intra-operative adhesion, C-reactive protein, white blood cell, monocyte/lymphocyte ratio

INTRODUCTION

Laparoscopic cholecystectomy (LC) is considered golden standard all over the world for the treatment of cholelithiasis (1).

LC can be used both for cholelithiasis cases and also for cases with acute cholecystitis. Adhesions developed as a result of inflammations and fibrosis in acute cholecystitis cases may cause difficulties during cholecystectomy. In these cases, there is risk of converting to open cholecystectomy.

Inflammation and fibrosis can be observed both in elective cholelithiasis and also in acute cholecystitis cases. Certain technical difficulties may arise during operation due to this inflammation and fibrosis. In these cases, it becomes difficult to discern anatomy, to dissect Calot's triangle, and uncontrolled bleeding and biliary tract injury may occur. Studies have shown that these factors are effective in conversion from laparoscopic cholecystectomy to open cholecystectomy (2).

CRP (C-reactive protein), procalcitonin, WBC (white blood cell) values are elevated in inflammation cases. Studies have shown that procalcitonin values higher than 1.5 ng/ml is a predictive value for difficult cholecystectomy (3). Furthermore, studies have shown that CRP value is the best inflammation marker to identify severity of acute cholecystitis and conversion to open cholecystectomy during operation (4).

The purpose of this study to predict technical difficulties during operation by comparing preoperative CRP, WBC, Monocyte/Lymphocyte ratio and intra-operative adhesion findings.

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MATERIAL AND METHOD

Ethical approval was obtained from the Hitit University Non-interventional Clinical Research Ethics Committee (Date: 30.04.2021, Decision No: 2021-66). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study includes 116 elective and emergency cholelithiasis cases whose operation performed at Corum Erol Olcok Training and Research Hospital in 2020 and 2021. All patients with their ages over 18 and who had undergone laparoscopic cholecystectomy by Members of Gastroenterology Surgery Subspeciality of Department of General Surgery between February 2020 and April 2021 were included in this study, and their data were collected from Hospital Data Management System retrospectively. Hospitals with ages under 18 and conversion cholecystectomy cases were excluded in this study. All cases were laparoscopically operated on by a single expert surgeon.

Data included in this study are age, gender, admission complaint, diagnosis, white blood cell count (WBC), monocyte count (MO), lymphocyte count (LY), platelet count (PLT), serum C-reactive protein level (CRP), additional diseases, emergency level of operation at the time of their admission, and time from admission to operation, operation duration, intra-operative adhesion grade, necessity to place drain and post-operative complication status. Monocyte and lymphocyte values and Monocyte/Lymphocyte ratio (MO/LY) were calculated and included as well.

Findings observed intra-operatively were graded by a single expert surgeon and recorded. Grades are defined as, Grade 1: No adhesion; Grade 2: light adhesion, peritoneal adipose tissue allowing easy dissection; Grade 3: chronic pericholecystitis and pericholecystic fibrosis, dissection is hard but anatomy can be traced; Grade 4: duodenum, colon adhesion to gallbladder causing anatomic distortion along with gallbladder wall thickening which does not allow safe dissection(5).

Patients were divided into two groups as Group 1: Grade 1-2 (n=84) and Group 2: Grade 3-4 (n=32) based on their intra-operative adhesion grades. WBC, CRP, MO/LY ratio, PLT and other parameters were compared between the groups in order to identify operation difficulty level.

Blood was drawn from patients preoperatively and laboratory tests were conducted on the samples. CRP, WBC and MO/LY ratios were recorded. Cholelithiasis status of each patient was confirmed via preoperative ultrasonography.

Groups graded based on intra-operative findings were compared with CRP, WBC and monocyte/lymphocyte ratio.

Statistical Analyses

Descriptive statistics such as age, gender, number of additional diseases were presented as number and percentage for categorical variables, and as mean±standard deviation or median (minimum-maximum) based on the data distribution for quantitative variables. Normal distribution of data was assessed with Shapiro Wilks test. Based on the distribution of the data, paired sampling t-test (Student's t-test) or Mann-Whitney U test was utilized for independent two groups and ANOVA or Kruskal-Wallis test was employed for more than two groups for the comparison of quantitative variables with the sociodemographic properties and research groups. Relationship between quantitative variables was investigated with Pearson or Spearman correlation coefficient based on data distribution. Ratio comparisons or correlation tests based on research groups were performed with Chi-square or Fisher exact test. Level of statistical significance was selected as $p<0.05$. Statistical analyses were performed by using IBM SPSS Statistics for Windows software (Version 26, IBM Corp., Armonk, N.Y., USA).

RESULTS

Out of total of 116 patients, 30 of them were male (25.9%) and 86 of them were female (74.1%). Age mean of entire patient group was found as 51.21±15.35 where median was 50.5, and youngest and oldest patients were 21 and 81 years old, respectively. In terms of additional diseases, 74 (63%) of the patients had no foreknown additional disease whereas 34 patients (29.3%) had 1 systemic disease and 8 patients (6.9%) had 2 systemic diseases.

The clinical features of the patients, comorbidities, grading of intraoperative adhesions, WBC, CRP, MO/LY mean, mean operation times and complications are summarized in **Table 1**.

Pre-operative and post-operative parameters were compared for the patients divided into two groups based on the adhesion grade as Grade 1-2 (n=84) and Grade 3-4 (n=32).

Most of the Group 1 patients with light adhesion were asymptomatic at the time of visit (71.4%), whereas abdominal pain was statistically significant for Group 2 patients ($p<0.001$) where adhesions were considerably higher. While cholelithiasis diagnosis was frequent in Grade 1-2 group patients (73.8%), cholecystitis diagnosis was more frequent in Grade 3-4 patients (75%) (**Table 2**).

Mean white blood cell count of Grade 3-4 group was mean 11.05±4.45 109/L and this value was statistically

significantly higher (p=0.01) than the mean value of Grade 1-2 group, which was found as 8.43±2.77 10^9/L. Similarly, mean C-reactive protein value of Grade 3-4 group was found as 50.91±77.25 mg/L and this value was significantly elevated (p<0.001) when compared with the mean values of Grade 1-2 group, which was found as 10.98±35.37 mg/L. Lymphocyte count was identified as 1.99±0.57 10^9/L for Grade 1-2 group and 1.48±0.70 10^9/L for Grade 3-4 group and difference was statistically significantly identified (p<0.001) (**Table 2**). Monocyte count was found as 0.63±0.24 109/L and 0.53±0.20 10^9/L for Grade 3-4 and Grade 1-2, respectively, and the difference, although high, was not statistically significant (p=0.055) (**Table 2**). Mean monocyte/lymphocyte ratio was found as 0.29±0.18 and 0.52±0.33 for Grade 1-2 and Grade 3-4 groups, respectively and these values were found statistically significant (p<0.001) (**Table 2**).

Operations were statistically significantly longer with 14 minutes longer for cases with high adhesion (57.19±19.42 min. for Grade 3-4 vs. 34.40±7.69 min. for Grade 1-2, p<0.001).

Adhesions were more frequent at emergency operations, however, there was no relation between duration until operation and observation of adhesions (p<0.001 and p=0.522, respectively).

Table 1. Properties of Entire Group

Entire Group (n=116)		
Gender	Male	30 (25.9%)
	Female	86 (74.1%)
Age		51.21±15.35 (50.50)
Number of Additional Disease	0	74 (63%)
	1	34 (29.3%)
	2	8 (6.9%)
Complaint	Asymptomatic	66 (56.9%)
	Abdominal Pain	48 (41.4%)
	Hepatitis	2 (1.7%)
Diagnosis	cholelithiasis	66 (56.9%)
	cholecystitis	38 (32.8%)
	Post-cholecystitis	4 (3.4%)
	Pancreatitis	8 (6.9%)
WBC		9.15±3.50 (8.00)
CRP		21.99±53.23 (3.42)
MO		0.56±0.22 (0.52)
LY		1.86±0.65 (1.93)
PLT		258.93±63.75 (245)
MO/LY		0.36±0.25 (0.25)
Operation Duration		40.69±15.78 (35)
Number of Open Surgery		44 (37.9%)
Duration Until Emergency Operation		3.45±1.48 (3)
Intra-operative Grade	1	58 (50%)
	2	26 (22.4%)
	3	16 (13.8%)
	4	16 (13.8%)
Necessity to place Drain		68 (58.6%)
Complication		6 (5.2%)

White blood cell count (WBC), monocyte count (MO), lymphocyte count (LY), platelet count (PLT), serum C-reactive protein (CRP), Monocyte/Lymphocyte ratio (MO/LY)

Table 2. Comparison of Grade 1-2 and Grade 3-4 Groups

Entire Group (n=116)				
Properties of Entire Group		**Grade 1-2 (n=84)**	**Grade 3-4 (n=32)**	**Statistical Significance**
Gender	Male	18 (21.4%)	12 (37.5%)	p=0.77
	Female	66 (78.6%)	20 (62.5%)	
Age		48.02±13.98 (46.50)	59.56±15.86 (63)	p<0.001
Number of additional disease	0	64 (76.2%)	10 (31.3%)	p<0.001
	1	18 (21.4%)	16 (50%)	
	2	2 (2.4%)	6 (18.8%)	
Complaint	Asymptomatic	60 (71.4%)	6 (18.8%)	p<0.001
	Abdominal pain	22 (26.2%)	26 (81.3%)	
	Hepatitis	2 (2.4%)	0 (0%)	
Diagnosis	cholelithiasis	62 (73.8%)	4 (12.5%)	p<0.001
	cholecystitis	14 (16.7%)	24 (75%)	
	Post-cholecystitis	2 (2.4%)	2 (6.3%)	
	Pancreatitis	6 (7.1%)	2 (6.3%)	
WBC		8.43±2.77 (7.70)	11.05±4.45 (10.06)	p=0.01
CRP		10.98±35.37 (3.13)	50.91±77.25 (16.50)	p<0.001
MO		0.53±0.20 (0.50)	0.63±0.24 (0.62)	p=0.055
LY		1.99±0.57 (2)	1.49±0.70 (1.35)	p<0.001
PLT		266.90±66.89 (248)	238.00±49.71 (240.50)	p=0.073
MO/LY		0.29±0.18 (0.22)	0.52±0.33 (0.42)	p<0.001
Operation duration		34.40±7.69 (35)	57.19±19.42 (47.50)	p<0.001
Number of open surgery		18 (21.4%)	26 (81.3%)	p<0.001
Duration until emergency operation		3.22±1.43 (3) (n=18)	3.62±1.52 (3) (n=26)	p=0.522
Necessity to place drain		36 (42.9%)	32 (100%)	p<0.001
Complication		2 (2.4%)	4 (12.5%)	p=0.28

White blood cell count (WBC), monocyte count (MO), lymphocyte count (LY), platelet count (PLT), serum C-reactive protein (CRP), Monocyte/Lymphocyte ratio (MO/LY)

Although drain was required to be placed to all of the patients with high adhesion grade was observed, only 36 of the patient (42.9%) of Grade 1-2 group were required drain placement (p<0.001). Number of complications were not statistically significant between groups (p=0.28). Since MO/LY ratio was statistically significantly different between groups, ROC analysis was performed in order to distinguish adhesion grades and area under the curve was calculated. Cutoff value sensitive and specific for differentiation of MO/LY ratio for the two groups was identified as 0.2693 with 81% sensitivity and 64% specificity (p<0.001).

Positive and negative predictive values were found as 46% and 90%. Performed risk analysis have shown that MO/LY value higher than 0.2693 have increased observation of adhesion 680% (OR 7.80 95% CI 2.888-21.067, p<0.001) (**Figure 1**) (**Table 3**) (**Table 4**).

As for WBC, 12.55 10^9/L value was 43.8 sensitive and 92.9% specific, and positive and negative predictive values were calculated as 70% and 81.3%, respectively. WBC values higher than 12.55 10^9/L have increase observation of adhesion 911% (OR 10.111 %95 CI 3.416-29.924, p<0.001) (**Figure 1**) (**Table 3**) (**Table 4**).

Cut-off value of 24.5 mg/L calculated for CRP value have shown to explain adhesion with 50% sensitivity and 97% specifity. Positive and negative predictive values were found as 88% and 83.7%. CRP values higher than 24.5 mg/L have increase observation of adhesion 4100% (95% CI 8.577-195.998, p<0.001) (**Figure 1**) (**Table 3**) (**Table 4**).

Table 3. Distribution of groups based on cut-off value

Inflammatory marker	Cut-off value	Entire Group		Statistical significance
		Grade 1-2 (n=84)	Grade 3-4 (n=32)	
MO/LY	<0.2693	54 (64.3%)	6 (18.8%)	p<0.001
	≥0.2693	30 (35.7%)	26 (81.2%)	
WBC	<12.55	78 (92.9%)	18 (56.3%)	p<0.001
	≥12.55	6 (7.1%)	14 (43.8%)	
CRP	<24.5	82 (97.6%)	16 (50%)	p<0.001
	≥24.5	2 (2.4%)	16 (50%)	

White blood cell count (WBC), serum C-reactive protein (CRP), Monocyte/Lymphocyte ratio (MO/LY)

DISCUSSION

Laparoscopic cholecystectomy has become golden standard both in elective cholelithiasis and also in acute cholecystitis cases. Operation would be harder especially in acute cholecystitis cases due to certain risk factors. However, as suggested at Tokyo Guideline 2018, laparoscopic cholecystectomy is the primary method of treatment in acute cholecystitis cases as well (6). Certain factors which causes gallbladder operation to be more difficult and causes conversion to cholecystectomy. Lipman et al. (7) Stated these factors as male gender, high WBC value, low albumin value, diabetic patient, pericholecystic fluid on ultrasonography, and high bilirubin value. Kama et al. (8), on the other hand, added previous surgery, acute cholecystitis, and increased gallbladder wall thickness on ultrasonography.

Operation is more difficult in acute cholecystitis cases than elective cholelithiasis cases. The main reason for this is difficult. visualization of anatomy due to intra-abdominal and perihepatic adhesions, and difficulty in dissection of Calot's triangle (5). The number of patients operated on due to acute cholecystitis was significantly higher in the group with higher grade of adhesion in our study as well.

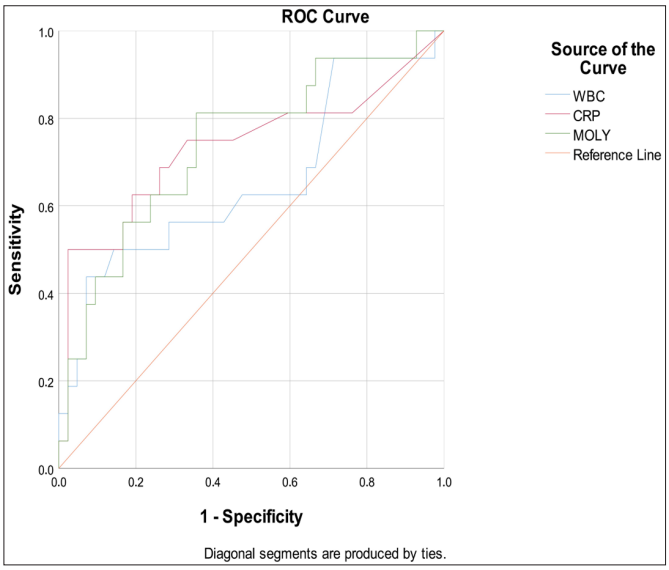

Figure 1. Diagonal segments are produced by ties.

Table 4. Diagnostic values and Odds Ratios of Markers

Inflammatory marker	Cut-off	Sensitivity	Specificity	PPV	NPV	ROC Analysis			Odds Ratio		
						Alan (SE)	%95 CI	p (ROC)	OR	95% CI	p (OR)
CRP	24.500	0.500	0.970	0.889	0.837	0.734 (0.061)	0.614-0.853	<0.001	41.000	8.577-195.998	<0.001
MO/LY	0.269	0.813	0.643	0.464	0.900	0.740 (0.054)	0.635-0.845	<0.001	7.800	2.888-21.067	<0.001
WBC	12.550	0.438	0.929	0.700	0.813	0.654 (0.062)	0.532-0.776	0.011	10.111	3.416-29.924	<0.001

White blood cell count (WBC), serum C-reactive protein (CRP), Monocyte/Lymphocyte ratio (MO/LY)

According to Lee et al. (9), old age is a predictive variable in difficult cholecystectomy. In our study, it was observed that elderly were grouped in higher adhesion group (Group 2) and therefore their operations were more difficult (G3-4:59.56±15.86 min. vs G1-2:48.02±13.98 min., p<0.001).

Studies have shown that elevated WBC is correlated with increase in acute cholecystitis and post-operative complications (10). Furthermore, elevated WBC is correlated with the severity of acute cholecystitis (6). However, no data could be identified in the literature regarding relationship between elevated WBC and gallbladder adhesions. In our study, WBC was identified to be statistically significantly higher in Grade 3-4 higher adhesions. Furthermore, the cut-off calculation have yielded 12.55 10^9/L value with 43.8% sensitivity and 92.9% specifity. Analyses have shown that WBC values higher than 12.55 10^9/L increases observation of adhesions on gallbladder 911%.

Similarly, CRP values higher than 30 g/L is considered to be a criteria for acute cholecystitis according to Tokyo Guidelines. However, according to Tokyo Guidelines, CRP value is not a criteria that identifies severity of acute cholecystitis. On the contrary, Beliaev et al. (11) considered CRP level as an important factor in identification of severity. Diaz-Flores et al. have mentioned that CRP values higher than 110 g/L is correlated with difficult laparoscopic cholecystectomy. Multivariant analyses conducted by Tianchong Wu et al. (12) concluded that CRP value is an effective factor in prediction of difficult laparoscopic cholecystectomy. In our study, CRP value was found to be statistically significantly higher (p<0.001) in highly adhesive group of Grade 3-4. Cutoff value of 24.5 mg/L calculated for CRP value have shown to explain adhesion with 50% sensitivity and 97% specifity. CRP value higher than 24.5 mg/L increases encountering intraoperative adhesion frequency 4100% (95% CI 8.577-195.998). This indicates that pre-operative CRP values higher than this cut-off value indicates a difficult laparoscopic cholecystectomy may occur.

Study conducted by Micic et al. found a relation between increasing neutrophile/lymphocyte ratio (NLR) and acute cholecystitis. This study reported that estimating NLR value higher than 4.18 pre-operatively is important to predict difficult cholecystectomy (13). The study conducted by Ahmed et al. (14) concludes that cases with NLR values higher than 5 had longer and more difficult cholecystectomy operation. The study conducted by Lee et al. (7) have concluded that high NLR values were observed in acute cholecystitis cases higher than chronic cholecystitis and mortality was observed more in cases with NLR values higher than 3. In our study, sensitive and specific Monocyte/lymphocyte ratio (Mo/Ly) cut-off value to differentiate the two groups was found as 0.2693 with 81% sensitivity and 64% specifity. Mo/Ly ratio higher than 0.2693 have increase observation of adhesion 911%. Furthermore, mean monocyte/lymphocyte ratio was found as 0.29±0.18 and 0.52±0.33 for Grade 1-2 and Grade 3-4 groups, respectively and these values were found statistically significant (p<0.001). Therefore, it can be predicted that cholelithiasis cases with Mo/Ly ratio higher than this cut-off value may cause operation to be more difficult due to advanced adhesions.

CONCLUSION

Adhesions on gallbladder, either acute cholecystitis or elective cholelithiasis, causes operation to be more difficult during laparoscopic cholecystectomy. Preoperative estimation of adhesion grade helps the surgeon considerably. This study shows that high CRP, WBC and Mo/Ly ratio values can help the estimation of intensity of adhesions and challenges during operation. We believe that this study shall pave way to more comprehensive studies in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Hitit University Non-interventional Clinical Research Ethics Committee (Date: 30.04.2021, Decision No: 2021-66).

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 approved the final version.

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REFERENCES

1. Navez, B, Prevention of bile duct injury (BDI) during cholecystectomy. Acta Chir Belg 2003; 103: 151-3.
2. Bingener-Casey, J, Richards ML, Strodel WE, Schwesinger WH, Sinirik KR. Reasons for conversion from laparoscopic to open cholecystectomy: a 10-year review. J Gastrointest Surg 2002; 6: 800-5.
3. Tianchong W, Minjun L, Yuehua G, Jiangang B, Yusheng G, Shiyun B. Role of procalcitonin as a predictor in difficult laparoscopic cholecystectomy for acute cholecystitis case: A retrospective study based on the TG18 criteria Observational Study Sci Rep 2019; 9: 10976.

4. Mahdi B, Slim Z, Bassem K, et al. C-reactive protein is the best biomarker to predict advanced acute cholecystitis and conversion to open surgery. a prospective cohort study of 556 cases. J Gastrointest Surg 2020; 24: 2766-72.
5. Ercan, M, Bostancı EB, Teke Z, et al. Predictive factors for conversion to open surgery in patients undergoing elective laparoscopic colecystectomy. J Laparoendosc Adv Surg Tech A 2010; 20: 427-34.
6. Wakabayashi, G, Iwashita Y, Hibi T, et al. Tokyo Guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci 2018; 25: 73-86.
7. Lipman JM, Claridge JA, Haridas M, et al., Preoperative findings predict conversion from laparoscopic to open cholecystectomy. Surgery 2007; 142: 556-63.
8. Kama NA, Doganay M, Dolapci M, Reis E, Atli, Kologlu M. Risk factors resulting in conversion of laparoscopic cholecystectomy to open surgery. Surg Endosc 2001; 15: 965-8.
9. Lee NW, Collins J, Britt R, Britt LD. Evaluation of preoperative risk factors for converting laparoscopic to open cholecystectomy. Am Surg 2012; 78: 831-3.
10. Agrawal N, Singh S , Khichy S. Preoperative prediction of difficult laparoscopic cholecystectomy: a scoring method. Niger J Surg 2015; 21: 130-3.
11. Beliaev A , Booth M. C-reactive protein as a diagnostic and prognostic marker for acute cholecystitis and safety conversion of laparoscopic cholecystectomy, in Advances in Medicine and Biology, Vol 101, L.V. Berhardt, Editor 2016, Nova Science Publishers. p. 15-37.
12. Wu T, Luo M, Guo Y, Bi J, Guo Y, Bao S. Role of procalcitonin as a predictor in difficult laparoscopic cholecystectomy for acute cholecystitis case: A retrospective study based on the TG18 criteria. Sci Rep 2019; 9: 10976.
13. Micic D, Stankovic S, Lalic N, Dukic V, Polovina S. Prognostic Value of Preoperative Neutrophil-to-lymphocyte Ratio for Prediction of Severe Cholecystitis. J Med Biochem 2018; 37: 121-7.
14. Ahmed SE, Rehman S, Edilbe M,Jonker L, Canelo R. Can neutrophil-lymphocyte ratio predict operators' difficulty in early cholecystectomies; a retrospective cohort study. Ann Emerg Surg 2017; 2: 1016.

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Exploring healthcare professionals' views and approaches regarding COVID-19 vaccines

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ABSTRACT

Aim: While going through tough times in the fight against the pandemic, healthcare professionals' approaches to vaccination may light a society's way. In our study, we aimed to investigate healthcare professionals' views on COVID-19 vaccines.

Material and Method: We carried out the study with a total of 500 voluntary healthcare professionals between January - April 2021. We administered a survey consisting of 15 multiple choice questions to the participants and put their responses into statistical analyses.

Results: There were a total of 500 participants, among whom 168 were males (33.6%). The mean age of the participants was 39.68 years (21-62). While the number of physicians was 48 (9.6%), there were 158 (31.6%) nurses and midwives and 294 (58.8%) other healthcare workers. Most of the participants (84.4%) thought COVID-19 to be a fatal infection. Again, the majority of participants believed in the necessity of vaccines (87%) and, especially, COVID-19 vaccines (73.2%). Besides, the rate of those vaccinated against COVID-19 was 82%. Interestingly, only about half of the participants (54%) believed in the protective effect of the vaccine. The participants pointed out ineffectiveness (34%) and side effects (28%) of vaccines as the frequent reasons for non-vaccination. Among those holding positive attitudes towards vaccines, 16.7% had not been vaccinated yet. A substantial rate of the participants (67.4%) recommended their acquaintances to get vaccinated against COVID-19, but 6.8% did not. Sixty-three percent of the participants would trust the locally developed vaccines more. Finally, 67% of the participants thought that vaccines would play a significant role in ending the pandemic.

Conclusion: In our study, we discovered that the vast majority of healthcare professionals were vaccinated against COVID-19 and adopted a positive approach towards vaccination. Overall, relevant education and informative programs may help increase the number of individuals adopting entirely positive attitudes towards COVID-19 vaccines.

Keywords: COVID-19 vaccines, healthcare professionals, survey, approach towards vaccines.

INTRODUCTION

COVID-19 is an infectious disease caused by SARS-CoV-2 and affecting the human respiratory system (1-3). It was first diagnosed in patients with severe pneumonia and flu-like symptoms in China (4). Its rapid and sudden spread has endangered health conditions of people and state economies across the world (5,6). Now, science has put forward advances in its treatment; however, an effective vaccine against the disease is still an urgent and vital need (7,8). It is essential not only because the vaccine may prevent the spread of the disease but also for recovering the social and economic affairs by ensuring herd immunity (9-17). On the one hand, scientists have attempted to develop vaccines, anti-vaccine voices, on the other hand, have the opportunity to reach large masses with the help of social media (18). Ultimately, evaluating the attitudes of healthcare professionals, having to fight against both the disease and vaccine opposition, towards vaccines is deemed critical as such attitudes may have an impact on public opinion. In this study, we explored healthcare professionals' views and approaches regarding COVID-19 vaccines adopting an unbiased perspective.

MATERIAL AND METHOD

We administered a survey consisting of 15 multiple choice questions to 500 healthcare professionals serving in our hospital (**Supplementary material-1**) and evaluated their responses. The participants were asked to read the questions carefully and mark the most appropriate option. When needed to collect the data face-to-face,

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we administered the surveys to the participants quickly, complying with the mask-hygiene-physical distance rule. In the survey, the participants were told that they could use their names or any nicknames, but we did not request their other personal information and kept their information confidential. We put the collected data into statistical analyses. All statistical analyses were performed using SPSS for Windows 15.0. We used the Chi-square test to assess parametric data (profession, gender), while it was the Mann-Whitney U test for non-parametric data.

Ethical approval was obtained from the Etlik Zübeyde Hanım Gynecology Training and Research Hospital Clinical Researchs Ethics Committee (Date: 05.26.2021, Decision No: 2021/57). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Finally, we received informed consent from all participants.

RESULTS

Overall Findings

We carried out all procedures in our study following the 1964 Helsinki Declaration and national/institutional ethical standards. Among the participants, 168 were males (33.6%). The mean age of the participants was 39.68 years (21-62). While the number of physicians was 48 (9.6%), there were 158 (31.6%) nurses and midwives and 294 (58.8%) other healthcare workers (**Figure 1**).

Analysis of the Responses

To the question "Do you think the COVID-19 is a fatal infection?", 84.4% answered "Yes," and 9.4% remained undecided. Then, the question "Who do you think COVID-19 may kill?" was responded to as "Everyone" (82%), "Only those with chronic diseases" (7%), and "Only immunocompromised individuals" (4.6%), respectively. While 54% answered "Yes" to the question "Do you think that COVID-19 vaccines provide full protection against the disease?", and 25% remained neutral. Statistically, we could not reach significant differences between these responses by gender (p=0.068) and profession (p=0.103).

While 73.2% of the participants thought COVID-19 vaccines to be necessary, 17.5% had no idea about the topic. Among those holding positive attitudes towards vaccination, 83.3% were vaccinated, but 16.7% were not. We could not find any significant differences between these responses by gender (p=0.441) and profession (p=0.434).

To the question "Do you think vaccines are overall necessary?", 87.0% answered "Yes." The rate of those who answered "Yes" to the question "Do you think COVID-19 vaccines are necessary?" was 73.2%. Interestingly, 18.2% of those believing in the necessity of vaccines did not think COVID-19 vaccines were needed. No significant difference was found between these responses by gender (p=0.726) and profession (p=0.434) (**Figure 2**).

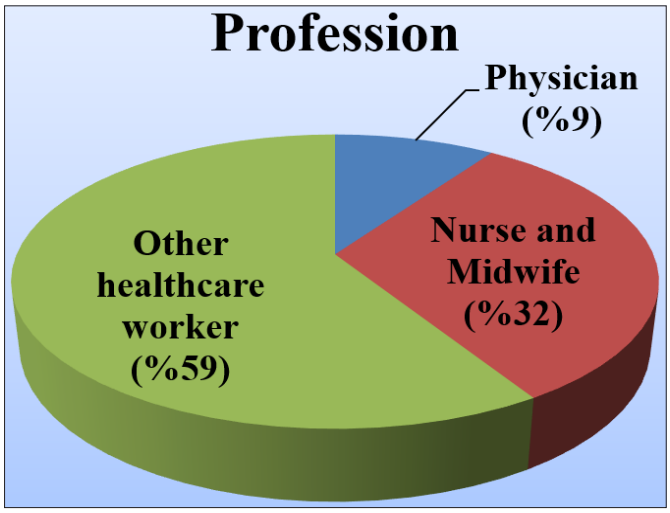

Figure 1. Distribution of the participants by profession

Supplementary material 1. Survey questions

Survey Questions
1. Do you think COVID-19 is a fatal infection?
2. Who do you think may COVID-19 kill?
3. Do you think that COVID-19 vaccines provide full protection against the disease?
4. Do you think COVID-19 vaccines are necessary?
5. Do you think vaccines are overall necessary?
6. Have any of COVID-19 vaccines shown any side effects on your relatives/acquaintances?
7. How do COVID-19 vaccines work?
8. Where have you got information about COVID-19 vaccines?
9. Do you recommend COVID-19 vaccines to your acquaintances?
10. What do you think is the most common side effect of COVID-19 vaccines?
11. Have you got vaccinated?
12. If not, what is your reason for not getting vaccinated?
13. Have you ever had any vaccine (such as influenza, pneumococcus) other than your childhood vaccines?
14. If a locally developed vaccine was introduced in our country, would you trust that vaccine?
15. Do you think vaccines will help end the pandemic?

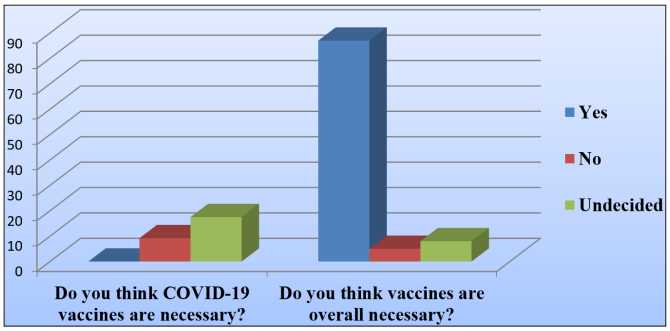

Figure 2. The participants' attitudes towards vaccines

About a quarter of the participants (14.6%) reported that their relatives developed some symptoms following vaccination. When asked "Where did you get the information about COVID-19 vaccines?", the participants pointed out media (28.8%) and their physicians (25%). The physicians answered this question mostly as "from scientific journals and publications," which differed significantly between physicians and other healthcare professionals in the study (p=0.003).

We also concluded that 67.4% of the participants recommended COVID-19 vaccines to their acquaintances. The male participants were found to be significantly more negative in this issue than their female counterparts (p=0.024). However, almost all participating physicians recommended vaccines to others (91.6%), and a significant difference was found between the physicians and others by vaccine recommendation (p=0.003). While 53.8% answered the question "What do you think is the most common side effect of the COVID-19 vaccine?" as "allergic reactions," 20.8% pointed out "influenza causing mortality." Other responses were shown in table (**Table 1**).

Table 1. Answers of the question "What do you think is the most common side effect of the COVID-19 vaccine"

Answers	Percentage (%)
Allergic reactions	53.8
Influenza causing mortality	20.8
Paralysis and neurological disorders	3.4
Heart failure	2.6
Infertility	1.4

The vast majority of the participants had already been vaccinated (82.0%). The vaccination rate was 91.0% among the physicians, 71.0% among nurses and midwives, and 74.0% among other healthcare workers. This rate was significantly higher in the physicians than in the other groups (p<0.001). When asked about the reason(s) for not getting vaccinated, the most common response was related to perceived ineffectiveness of vaccines (34%). This response was followed by thoughts that vaccines have many side effects (28%) and that people can protect themselves against COVID-19 only by using a mask and complying with the physical distance rule (25%) (**Table 2**).

Table 2. Reasons for not getting vaccinated

Reason	Percentage %
Vaccines are ineffective	34
Vaccines have many side effects	28
People can protect themselves by complying only with the mask-hygiene-distance rule	25
I have experienced severe side effects of previous vaccines	3
I am allergic to vaccines	10

Among the participants, 63% stated that they would trust locally developed vaccines more, but 30.3% would still remain neutral. While 67% of the participants thought that vaccines would help end the pandemic, 10% did not.

DISCUSSION

The denying approach to vaccines, which are the most critical weapons in combating infectious diseases, has been on the agenda since the very first day vaccines were introduced (18,19). Defined as behavior patterns ranging from being against a specific vaccine to rejecting all vaccines, vaccine opposition threatens community health (19). The most damaging vaccine deception of the last century has been the article published in "The Lancet," which reports a so-called association between the measles vaccine and autism (19,20). Although it was realized that the study data were falsified, which led it to be removed from publication, it caused a decrease in the reliability of the measles vaccine and an increase in measles in the population (20). Besides, the unstoppable rise in sharing health-related issues on social media causes information pollution and helps the rapid spread of misinformation, which can provoke anti-vaccination (19,20).

On the other hand, it is known that informing families by healthcare professionals contributes to vaccination rates, which implies that healthcare professionals have a critical role in families' decisions on the vaccination of their children (21,22). In a study by the European Center for Disease Prevention and Control group in 2015 to identify vaccine hesitancy among healthcare workers and their patients, the most reliable source of information on vaccines was found to be healthcare professionals (23).

In our study, 6.2% of the participants thought the COVID-19 infection was not fatal, while 9.4% remained neutral. In a study by Ergün et al. (24), the participating healthcare professionals were asked how adequately they considered their COVID-19-oriented knowledge. Accordingly, they concluded that the majority of the participants (80%) found their knowledge adequate. The idea that the COVID-19 infection is not fatal among healthcare professionals, despite working in hospitals and seeing deaths from COVID-19, may be because they have insufficient knowledge on the subject.

In our study, 54% thought COVID-19 vaccines would provide robust protection against the disease, while 21% thought vice versa, and 25% remained undecided. However, those who were unsure about the protection of vaccines also got vaccinated (82%). Interestingly, we determined that 16.7% of those thinking vaccines were needed did not get vaccinated, which may be due to vaccine hesitancy of people.

In the study of Arslanca et al. (25), 66.93% of the healthcare professionals considered getting vaccinated against COVID-19, and 10.36% remained undecided. Brunon et al. (26) determined a positive approach towards COVID-19 vaccines at a rate of 75% among healthcare professionals. The rate of positive approach towards the seasonal flu vaccine among the participants was reported to be 57.3% in the previous season. In our study, we determined that 18% of the participants were not vaccinated, and this rate was higher among non-physician healthcare workers.

Dror et al. (27) found that physicians had significantly more positive attitudes towards COVID-19 vaccines than nurses (73% vs. 61%, respectively) . Vaccination may be counted among the most important factors to be able to end such a global crisis, so it seems healthcare professionals need to engage in a continuous update of their knowledge, which may contribute to the rise of vaccination rates. In a study by Ünal et al. (28), family physicians were recruited for one-day training by infectious diseases and internal medicine specialists. The cross-sectional data obtained six months after the program revealed that the vaccination rate among the participants increased from 33.9% to 45.5%.

The same study by Dror et al. (27) also revealed that the male participants accepted vaccination more, which may be because men are more prone to COVID-19 or some diseases considered risk factors for COVID-19, such as cardiovascular diseases, cancer, or chronic respiratory diseases, appear more in men. Lazarus et al. (29) carried out a study with 13,426 participants from 19 countries and asked the participants, "Do you think COVID-19 vaccines are helpful?" Overall, 46.8% strongly agreed, 24.7% partially agreed, 14.2% had no idea, and 8.1% did not agree with the question. In our study, about one-third of the participants (34%) assumed COVID-19 vaccines were ineffective, which was the most important reason for non-vaccination. Other reasons were "vaccines have many side effects" (28%) and "mask-hygiene-distance rule is the best to be protected from the disease" (25%).

In the study by Dror et al. (27), both healthcare professionals and other people commonly adopted concerns about the quality and side effects of vaccines because they were developed rapidly. Biswas et al. (30) found that the most common reasons uttered by healthcare professionals who did not want to get vaccinated were related to hesitations about the effectiveness, safety, and side effects of vaccines. The researchers concluded insufficient knowledge about vaccines and perception of COVID-19 not to be a severe disease as other reasons for non-vaccination. In the study of Arslanca et al. (25), all participants thought COVID-19 to be a fatal infection. Although the reasons for not getting vaccinated showed a similarity between our study and the literature, the rate of considering COVID-19 to be a fatal infection was a bit different in our study (84.4%).

Lucia et al. (31) performed a study with 168 medical students in the United States and found that 76.7% of the participants had concerns about the effect of COVID-19 vaccines. In addition, this rate was found to be 83.8% among those who were reluctant to participate in a vaccine trial. In our country, few studies explored the attitudes of healthcare professionals and people towards the flu vaccine. In their study with 371 participants, Kul et al. (32) found that the participants showed the reasons for not having the flu vaccine as disbelief in the necessity of vaccines (26.0%), preferring other prevention methods (22.1%), fear of its side effects (18.3%), and inadequate trial of the vaccine (11.4%). Sarı et al. (33) documented different rates of these reasons: disbelief in the necessity of vaccines (64.5%), preferring other prevention methods (40.9%), and fear of its side effects (39.1%).

Almost all of the participants (98%) in the study by Lucia et al. (31) stated that COVID-19 vaccines were vital in preventing the spread of the disease, but only 53% would agree to participate in a vaccine trial. In addition, this rate was found to be higher among clinical students than preclinical students. In the same study, the rate of those thinking that vaccination against COVID-19 should be mandatory for the public was 67.9%, while 85.9% thought it should be mandatory for healthcare workers (31). In our study, most of the participants (87%) thought vaccines were overall necessary, but this rate slightly dropped when it came to COVID-19 vaccines (73.2%). Among those who believed that vaccines were overall needed, 18.2% considered COVID-19 vaccines were unnecessary. About a quarter of the participants (13%) found vaccines unnecessary, which indicates that anti-vaccine views exist even among healthcare professionals. Relevant education programs, positive campaigns on social media, and vaccination-friendly policies may contribute to the elimination of vaccine opposition.

Dror et al. (27) concluded the participating healthcare professionals had much lower acceptance rates of COVID-19 vaccines than the flu vaccine. Also, it was determined that those who had a seasonal flu vaccine adopted more positive approaches towards COVID-19

vaccines. In the research by Lazarus, 31.9% strongly agreed, 9.8% strongly disagreed, and 20.6% were undecided with the question, "If a COVID-19 vaccine was announced to be safe and effective and recommended by the government, would you accept it?" (29). In our study, 63% of the participants would trust locally-developed vaccines more, while 30.3% remained neutral. Finally, while 67% of the participants thought vaccines would help end the pandemic, 10% stated that they would not be effective.

CONCLUSION

During the pandemic, healthcare professionals had to fight the disease, as well as struggling with the increasing vaccine opposition. Therefore, healthcare professionals' views on vaccines may guide public opinion on vaccines. Our results suggested that the majority of the participants had positive approaches to vaccines. Accordingly, relevant education programs on vaccines may help foster such desirable approaches and have intended impacts on vaccination rates.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Etlik Zübeyde Hanım Gynecology Training and Research Hospital Clinical Researchs Ethics Committee (Date: 05.26.2021, Decision No: 2021/57)

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 approved the final version.

Acknowledgment: A part of this study was presented as an oral presentation at the 9th Turkey Ekmud Scientific Platform on May 22, 2021.

REFERENCES

1. Taleghani N, Taghipour F. Diagnosis of COVID-19 for controlling the pandemic: A review of the state-of-the-art. Biosens Bioelectron 2021; 174: 112830.
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. Umakanthan S, Sahu P, Ranade AV, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). Postgrad Med J 2020; 96: 753-8.
4. Yüce M, Filiztekin E, Özkaya KG. COVID-19 diagnosis - A review of current methods. Biosens Bioelectron 2021; 172: 112752.
5. Habas K, Nganwuchu C, Shahzad F, et al. Resolution of coronavirus disease 2019 (COVID-19). Expert Rev Anti Infect Ther 2020; 18: 1201-11.
6. Islam KU, Iqbal J. An Update on Molecular Diagnostics for COVID-19. Front Cell Infect Microbiol 2020; 10: 560616.
7. Soleimanpour S, Yaghoubi A. COVID-19 vaccine: where are we now and where should we go? Expert Rev Vaccines 2021; 20: 23-44.
8. Awadasseid A, Wu Y, Tanaka Y, Zhang W. Current advances in the development of SARS-CoV-2 vaccines. Int J Biol Sci 2021; 17: 8-19.
9. Sharma NK, Sarode SC, Sarode G, Patil S. Is a COVID-19 vaccine developed by nature already at work? Med Hypotheses 2020; 145: 110335.
10. Sreepadmanabh M, Sahu AK, Chande A. COVID-19: Advances in diagnostic tools, treatment strategies, and vaccine development. J Biosci 2020; 45: 148.
11. Li YD, Chi WY, Su JH, Ferrall L, Hung CF, Wu TC. Coronavirus vaccine development: from SARS and MERS to COVID-19. J Biomed Sci 2020; 27: 104.
12. Silveira MM, Moreira GMSG, Mendonça M. DNA vaccines against COVID-19: Perspectives and challenges. Life Sci 2021; 267: 118919.
13. Mehrotra DV, Janes HE, Fleming TR, et al. Clinical Endpoints for evaluating efficacy in COVID-19 vaccine trials. Ann Intern Med 2021; 174: 221-8.
14. Marian AJ. Current state of vaccine development and targeted therapies for COVID-19: impact of basic science discoveries. Cardiovasc Pathol 2021; 50: 107278.
15. Liu X, Liu C, Liu G, Luo W, Xia N. COVID-19: Progress in diagnostics, therapy and vaccination. Theranostics 2020; 10: 7821-35.
16. Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: The status and perspectives in delivery points of view. Adv Drug Deliv Rev 2021; 170: 1-25.
17. Halstead SB, Katzelnick L. COVID-19 Vaccines: Should We Fear ADE? J Infect Dis 2020; 222: 1946-50.
18. Omer SB, Salmon DA, Orenstein WA, deHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. N Engl J Med 2009; 360: 1981-8.
19. Kader Ç. Aşı Karşıtlığı: Aşı Kararsızlığı Ve Aşı Reddi. ESTÜDAM Halk Sağlığı Dergisi 2019; 4: 377-88.
20. Wakefield A, Murch S, Anthony A, et al. İleal-lenfoid-nodülerhiperplazi, spesifik olmayan kolit ve çocuklarda yaygın gelişimsel bozukluk. Lancet 1998; 351: 637–41.
21. Puri N, Coomes EA, Haghbayan H, Gunaratne K. Social media and vaccine hesitancy: new updates for the era of COVID-19 and globalized infectious diseases. Hum VaccinImmunother 2020; 16: 2586-93.
22. Argüt N, Yetim A, Gökçay G. Aşı kabulünü etkileyen faktörler. Çocuk Derg 2016; 16: 16-24.
23. Karafillakis E, Dinca I, Apfel F, et al. Vaccine hesitancy among healthcare workers and their patients in Europe: A Qualitative Study. Vaccine 2016; 34: 5013-20.
24. Ergün E, Ergün Ş, Çelebi İ. Acil Sağlık Hizmetleri Personellerinin COVID-19 Hakkında Bilgi, Korunma Düzeyleri Ve Etkileyen Etmenler. JOPEHS 2020; 1: 16-27.
25. Arslanca T, Fidan C, Daggez M, Dursun P. Knowledge, preventive behaviors and risk perception of the COVID-19 pandemic: A cross-sectional study in Turkish health care workers. PLoS One 2021; 16: e0250017.
26. Gagneux-Brunon A, Detoc M, Bruel S, et al. Intention to get vaccinations against COVID-19 in French healthcare workers during the first pandemic wave: a cross-sectional survey. J Hosp Infect 2021; 108: 168-73.

27. Dror AA, Eisenbach N, Taiber S, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. Eur J Epidemiol 2020; 35: 775-9.
28. Ünal S , Tanrıöver MD, Taş E, Güner İ, Çetin ÖY, Sayar İ. Aile Hekimlerine Eğitim Verilmesi Ve Aşılama Hedeflerinin Belirlenmesinin Pnömokok Aşılanma Oranları Üzerine Etkileri. FLORA 2015; 20: 10-15
29. Lazarus JV, Ratzan SC, Palayew A, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med 2021; 27: 225-8.
30. Biswas N, Mustapha T, Khubchandani J, Price JH. The nature and extent of COVID-19 vaccination hesitancy in healthcare workers. J Community Health 2021; 20: 1–8.
31. Lucia VC, Kelekar A, Afonso NM. COVID-19 vaccine hesitancy among medical students. J Public Health (Oxf) 2020: fdaa230.
32. Kul G, Korkmaz N. Sağlık Çalışanlarının İnfluenza Aşılamasına Yaklaşımı. J Contemp Med 2020; 10: 421-4.
33. Sarı T, Temoçin F, Köse H. Sağlık çalışanlarının influenza aşısına yaklaşımları. Türkiye Klinik Derg 2017; 30: 59-63.

Original Article

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The effect of blood gas analysis and Charlson comorbidity index evaluation on the prediction of hospitalization period in patients with diabetic hyperglycemic crisis

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ABSTRACT

Objective: This study aims to evaluate the effectiveness of blood gas analysis at the time of admission and additional Charlson comorbidity index (CCI) in predicting the hospitalization period of patients admitted to the emergency department (ED) with a hyperglycemic crisis.

Material and Method: This study was designed as retrospective, cross-sectional and observational. The patients who admitted to the ED with hyperglycemic crisis (diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome) and hospitalized were included in the study within 2 years between January 1, 2019, and January 1, 2021, in a tertiary research hospital

Results: A total of 93 patients included in this study, which of 48 (51.6%) were female and 45 (48.4%) were male. The mean age of the patients was 63.49±26.59. The mean hospitalization period was determined as 6.25±5.16 days. In total, 7 patients (7.5%) were followed up in the intensive care unit (ICU), while mortality was observed in 2 (2.15%) of these patients. It was determined that there was a statistically significant association between hospitalization period of the patients and their findings such as age (r=0.879, p<0.001), Charlson index (r=0.708, p<0.001), PH value (r=0.312, 0.002), HCO_3 value (r=0.316, p=0.002), BE value (r=-0.315, p=0.002).

Conclusion: It can be predicted that patients who admitted to the ED with DKA and HHS will have a long hospitalization according to blood gas analysis evaluation and presence of comorbidities. Additionally, the quality of treatment can be increased by measures such as education, early consultation of the diabetes team and early detection of triggering factors.

Keywords: Blood gas analysis, diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, length of stay, emergency department

INTRODUCTION

Diabetes is a disease that affects public health with a rising trend in the world. According to the World Health Organization (WHO) data, it is the 9th most common cause of mortality worldwide in 2019 (1), and it caused an economic burden of approximately 327 billion dollars with 40.3 million patients in the USA in 2017. therefore, It is required to be controlled since both its high cost and the loss of workforce. It has been revealed that uncontrolled diabetes patients have negative outcomes such as extension of hospitalization, increased mortality and morbidity (2). Studies are reporting that even the presence of diabetes alone causes side effects on many systems of the human body (3). There are many studies conducted to predict these side effects (4,5). However, the fact that 25-30% of all hospitalized patients are diagnosed with diabetes reveals that diabetes alone is an important factor that should be evaluated during hospitalization (6). Acute glycemic changes have been proved to be the primary cause in 4-9% of hospitalized diabetes patients.

In this determination, mainly two clinical syndromes emerged. Diabetic ketoacidosis (DKA) and Hyperosmolar hyperglycemic state (HHS) are the most severe acute metabolic complications of diabetes (6). The DKA is one of the preeminent hyperglycemic complications related to diabetes (7) and consists of metabolic acidosis, hyperlactatemia, ketonuria and ketonemia (8). It is caused for more than 500,000 hospitalizations by a year (9). Hyperosmolar hyperglycemic syndrome (HHS) is characterized by high glucose and osmolarity, as well as the absence of ketoacidosis (10). Relative insulin deficiency in HHS causes more osmotic diuresis and dehydration than DKA (11).

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These 2 clinical conditions are important metabolic conditions that may cause diabetic patients to admitted with hyperglycemic coma. In fact, in DKA and HHS, besides insulin deficiency, it occurs as a result of an increase in counterregulatory hormones (glucagon, catecholamines, cortisol and growth hormone). The increase in these counterregulatory hormone levels also causes different hemodynamic and metabolic disorders. This is another cause why the clinical course of patients is challenging to manage. Therefore, DKA and HHS are syndromes that endanger patient life and require urgent hospitalization. Predicting the hospitalization period in these patients is important in terms of more aggressive approaches in treatment modalities, and earlier evaluation of patients by endocrinology specialists or a diabetes team (12). However, these rates reveal different results such as 3-13% in developing countries, in children or individuals over 60 years of age with comorbid diseases (13-15). Mortality rates due to HHS vary as 5-16%. The high mortality rates of both clinical conditions are required early intervention (12).

It has been not revealed a gold standard method for evaluating the effects of comorbid diseases on mortality and hospitalization period. However, the CCI has been practiced for many years to evaluate the effects of comorbid diseases on mortality, re-admission, and hospitalization period (16). The updated CCI evaluates 12 comorbid diseases (17). Comorbidities are scored from 1 to 6 to assess mortality risk and disease severity. Conclusively, these values are summed for each patient and the total score is reached. In patients with a CCI score of 5 and above, while 1-year mortality was found as 85%, the 10-year survival was found as 34% (16).

The primary aim of our study is to evaluate the effect of blood gas analysis and comorbidities in predicting the hospitalization period of patients admitted to the ED with a hyperglycemic crisis.

MATERIAL AND METHOD

Ethics committee approval was obtained from Health Sciences University, Kartal Dr. Lütfi Kırdar City Hospital Non-interventional Research Ethics Committee (Date: 28.04.2021, Decision No: 2021/514/200/22) granted the relevant approval to our study. We carefully minded that all procedures applied in this study complied with the 1964 Helsinki Declaration and the ethical standards of the National/Institutional Scientific Research Committee.

Patients

This study was designed as a retrospective, cross-sectional and observational. The patients who admitted to the ED with hyperglycemic crisis (diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome) were included in the study within 2 years between January 1, 2019, and January 1, 2021, in a tertiary research hospital.

In the first blood gasses of the patients at the time of admission, the values such as pH, PCO_2, lactate, base deficit, HCO_3 and disease histories and risk of comorbidities were scanned from the hospital automation system. All patients were treated with standard approaches in the ED. Blood gas analyzes of all patients have performed with the ABL 800 FLEX blood gas analyzer (Radiometer, Copenhagen, Denmark) device. It was researched whether the patients had a chronic disease such as hypertension, myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, chronic liver disease, hemiplegia, chronic kidney disease, solid tumour, leukaemia and lymphoma in their disease histories. CCI values were then calculated using these data.

Inclusion Criteria

Being over 18 years old and being admitted to the ED with hyperglycemic crisis (diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome) with ICD codes [E10.1, E11.1, or E13.1 (diabetic ketoacidosis) or E11.0, E13.0, or E10.65 and E10.69 (hyperosmolar hyperglycemic syndrome)], after diagnosed and hospitalized.

Exclusion Criteria

Being under the age of 18 and being the one whose disease histories could not be reached by blood tests from the hospital automation system.

When diagnosing DK and hyperosmolar hyperglycemic syndrome, the guidelines of the American Diabetes Association were based on (10). For DK, plasma glucose >250 mg/dl, arterial pH<7.3 serum HCO_3 <18, urine ketone positivity criteria are accepted, for the hyperosmolar hyperglycemic syndrome, glucose level >600 mg/dL, plasma effective osmolarity >320 mOsm/L, and an absence of significant ketoacidosis was accepted (10). The CCI scores of the patients were calculated using MedCalc 12.3.0.0 for Windows (MedCalc Software, Mariakerke, Belgium). The sample size in the study was calculated by considering both the number of in-hospital patients for 2 years and the numbers in similar studies (19).

Statistical Analysis

R version 2.15.3 program (R Core Team, 2013) was performed for statistical analysis. Minimum, maximum, mean, standard deviation, median, first quartile, third quartile, frequency and percentage were used when reporting the study data. The conformity of the quantitative data to the normal distribution was assessed with the Shapiro-Wilk test and graphical examinations. The Mann-Whitney U test was practiced to evaluate the variables that did not show normal distribution between the two groups. Pearson correlation analysis was used to determine the level of association between quantitative variables. Statistical significance was accepted as $p<0.05$.

RESULTS

After scanning the data of patients with ICD codes from the hospital automation system, the information of 96 patients were reached. One patient whose disease history data could not be reached and two patients who were transferred to another hospital during the treatment period were excluded from the study. There were 93 patients included in the study, which of 48 were female (51.6%) and 45 were male (48.4%). The mean age of the patients was 63.49±26.59. The mean hospitalization period was determined as 6.25±5.16 days. In total, 7 patients (7.5%) followed up in the ICU, while mortality was observed in 2 patients (2.15%) (**Table 1**). It was determined that there was a statistically significant association between hospitalization period of the patients and their findings such as age (r=0.879, p<0.001), Charlson index (r=0.708, p<0.001), pH value (r=0.312, 0.002), HCO_3 value (r=0.316, p=0.002), BE value (r=-0.315, p=0.002). There was no statistically significant correlation was found between the hospitalization period and the lactate and PCO_2 values in blood gas at the time of admission (p>0.05). There was no statistically significant difference in terms of hospitalization period according to gender and ICU condition of the cases (p>0.05) (**Table 2**).

Table 1. Characteristics of patients

	Min-Max	Mean±ss
Age	18-109	63.49±26.59
Hospitalization period	1-25	6.25±5.16
Charlson index	2-9	2.73±1.35
PH	6.91-7.49	7.3±0.14
Lactate	0.7-6.7	2.51±1.18
HCO_3	5.5-30.1	19.67±7.05
BE	0-28	8.08±8.28
PCO_2	9.1-58.6	37.28±11.66
	n	**%**
Gender		
Female	48	51.6
Male	45	48.4
Mortality	2	2.15
ICU	7	7.5
HT	42	45.2
SVO	4	4.3
KBY	2	2.2
Cirrhosis	0	0.0
Malignancy	7	7.5
KKY	7	7.5
COPD	4	4.3
Alzheimer/demands	0	0.0
Immune suppression	1	1.1
Rheumatic diseases	2	2.2
Hemiplegia/paraplegia	0	0.0
Peripheral vascular disease	1	1.1

Table 2. The association of blood gas and CCI with hospitalization period

	r	[a]p
Age	0.879	<0.001*
Charlson index	0.708	<0.001*
PH	0.312	0.002*
Lactate	0.133	0.203
HCO_3	0.316	0.002*
BE	-0.315	0.002*
PCO_2	0.199	0.055
	Median (Q1, Q3)	**[b]p**
Gender		0.126
Female	5 (3, 9)	
Male	3 (2, 8)	
ICU		0.216
No	4 (3, 8)	
Yes	11 (1, 14)	

[a]Pearson correlation analysis, [b]Mann-Whitney U test, results are presented (as first quarter, third quarter). *p<0.0

DISCUSSION

In this study, which evaluated the prediction of hospitalization period and blood gas at the time of admission to the ED, a strong correlation was found between especially age, Ph, HcO_3, BE and CCI (p<0.005). According to these results, the requirement for longer hospitalization in the early period can be predicted by evaluating the blood gases at the time of admission and additional diseases of the patients. This knowledge can lead to changes in patient management.

Diabetes is a complex and chronic disease that requires constant medical support (20). Diabetic hyperglycemic crisis patients are diagnosed after their admission to the ED and treated according to standard approaches. However, the treatment period can be completed by following many different factors together (21). Early prediction of hospitalization period, evaluation by the diabetes team, education, and prevention of triggering events to prevent future attacks are significant precautions (21). When all these precautions are completed, the treatment will be completed (21). Thus, it can contribute to reducing the economic burden of diabetic patients on the health system and relieving the workforce.

Important limitations of this research are that it was a retrospective study and evaluated a limited population of patients.

The blood gas analysis is a rapid, inexpensive and effective test in evaluating the patient. It is practiced to evaluate the metabolic status in the diagnosis of DKA and HHS. There are studies in the literature determining the relationship between blood gas variables and 30-day mortality, especially in DKA (22). In a single-center study involving a limited population, lactate clearance in the first two hours was associated with 30-day mortality (22).

CCI calculates a score based on patients' age and comorbidities. It uses it to predict patients' in-hospital-, 1-year and 10-year mortality. CCI is objective and covers both systemic and localized disease while allowing for the adjustment of age (23).

In our study, it was determined that the changes in Ph, HCO_3, BE values in the blood gas analysis were significantly associated with the hospitalization period. According to the conclusions of our study, potential increase in hospitalization period may be predicted by the blood gas analysis and additional disease information that can be easily accessed after the ED admission of the patients. The current guideline of the American Diabetes Association suggests that all patients hospitalized for diabetes should be assessed by a specialized diabetes team in the early stage (24,25). In a study evaluating the effect of diabetology consultation in the first 48 hours on the hospitalization period, it was determined that the average hospitalization period of the patients who were consulted was 1.56 days less (26). According to this result and our study, the average hospitalization period can be shortened if the first blood gas analysis and comorbidities and the patients who are predicted to be a long hospitalization period are recognized in the early period and a diabetes consultation is performed. Cost-effectiveness can also be achieved with measures to be taken especially in the management of patients who are expected to have a long hospitalization period.

CONCLUSION

It can be predicted that patients who admitted to the ED with DKA and HHS will have a long hospitalization period according to blood gas analysis evaluation and presence of comorbid diseases. In particular, there is a strong correlation between the patient's age and the Ph, HcO_3, BE blood gas at the time of admission and CCI. Factors such as patient education and early evaluation by the diabetes team may shorten the hospitalization period.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from Kartal Dr. Lütfi Kırdar City Hospital Non-interventional Researchs Ethics Committee (Date: 28.04.2021, Decision No: 2021/514/200/22)

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. Diabetes Care 2018; 41: 2648-68.
2. Endocrinologists AAoC. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 2009; 32.
3. Kalkan S, Karatay E, Akbal E. Increased gastrointestinal symptom frequency in diabetes mellitus even with good glycemic control.J Health Sci Med 2020; 3: 26-30.
4. Yiğenoğlu TN, KEBAPÇI MN, Hülya Ö. The significance of ankle-brachial index in determining peripheral artery disease in patients with type 2 diabetes mellitus over 40 years of age and the relationship of peripheral artery disease with chronic complications of diabetes. J Health Sci Med 2020; 3: 115-20.
5. Handan A, YILMAZ S, Can FK, Parlak M. An evaluation of risk factors affecting amputation in patients with diabetic foot Infection. J Health Sci Med 2021; 4: 49-54.
6. Draznin B, Gilden J, Golden S, Inzucchi S, Baldwin D, Bode B. for the PRIDE investigators. Pathways to quality inpatient management of hyperglycemia and diabetes: a call to action Diabetes Care 2013; 36: 1807-14.
7. Kitabchi AE, Wall BM. Diabetic ketoacidosis. Med Clin North Am 1995; 79: 9-37.
8. Gosmanov AR, Gosmanova EO, Dillard-Cannon E. Management of adult diabetic ketoacidosis. Diabetes Metab Syndr Obes 2014; 7: 255.
9. Kim S. Burden of hospitalizations primarily due to uncontrolled diabetes: implications of inadequate primary health care in the United States. Diabetes care 2007; 30: 1281-2.
10. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes care 2009; 32: 1335-43.
11. Patel M. Emergencies in diabetes–diabetic ketoacidosis and hyperosmolar hyperglycaemic state. Medicine 2020; 49: 106-9.
12. Umpierrez G, Korytkowski M. Diabetic emergencies—ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol 2016; 12: 222.
13. Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality—United States, 2000–2014. Morbidity and Mortality Weekly Report 2018; 67: 362.
14. Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998–2013: a retrospective cohort study. Diabetes Care 2018; 41: 1870-7.
15. Poovazhagi V. Risk factors for mortality in children with diabetic keto acidosis from developing countries. World J Diabetes 2014; 5: 932.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-83.
17. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries.Am J Epidemiol 2011; 173: 676-82.
18. Lange SJ, Ritchey MD, Goodman AB, Dias T, Twentyman E, Fuld J, et al. Potential indirect effects of the COVID-19 pandemic on use of emergency departments for acute life-threatening conditions—United States, January–May 2020. Wiley Online Library; 2020.
19. Siregar NN, Soewondo P, Subekti I, Muhadi M. Seventy-two hour mortality prediction model in patients with diabetic ketoacidosis: a retrospective cohort study. J ASEAN Fed Endocr Soc 2018; 33: 124.

20. Riddle MC, Bakris G, Blonde L, Boulton A. American Diabetes Association standards of medical care in diabetes–2019. Diabetes Care 2019; 42: 34-60.
21. French EK, Donihi AC, Korytkowski MT. Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients. Bmj 2019; 365: I1114.
22. Ibrahim A, Bayramoglu B, Hokenek NM, Tekyol D. Lactate clearance during the first 2 hours after hospital admission: A useful biomarker for predicting 30-day mortality in patients with diabetic ketoacidosis. Int J Clin Pract 2021: e14204.
23. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011; 173: 676-82.
24. Bansal V, Mottalib A, Pawar TK, et al. Inpatient diabetes management by specialized diabetes team versus primary service team in non-critical care units: impact on 30-day readmission rate and hospital cost. Bmj Open Diab Res Ca 2018; 6.
25. Flanagan D, Moore E, Baker S, Wright D, Lynch P. Diabetes care in hospital—the impact of a dedicated inpatient care team. Diabet Med 2008; 25: 147-51.
26. Sheahan KH, Atherly A, Dayman C, Schnure J. The impact of diabetology consultations on length of stay in hospitalized patients with diabetes.Endocrinol Diabetes Metab 2021; 4: e00199.

Original Article

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The effect of vertebral artery characteristics on cervical discogenic pain and disability

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ABSTRACT

Objective : Cervical discogenic pain, which is characterized by a stiffness or pain in neck movement, generally occurs as a result of disc degeneration. On the other hand; vascular pathologies of the cervical region, especially vertebrobasilar insufficiency, may give rise to similar findings in patients; it can also be detected simultaneously with cervical disc pathologies. In this study, it was aimed to investigate whether the circulatory properties of the vertebral arteries have an effect on the neck pain and functional status of the patients.

Material and Method: Based on the participants' medical history, physical examination and radiological examination, sixty five patients were diagnosed with cervical disc herniation. Twenty patients who met the inclusion criteria were completed the study. Vertebral artery and carotid artery doppler ultrasonography was performed in these patients, thus any stenosis or insufficiency in vascular systems of the neck was evaluated. Additionally; vertebral blood flow rate (ml/min),vessel diameter(mm), minimum blood flow velocity (Vmin) and maximum blood flow velocity (Vmax) was measured by doppler ultrasonography. The obtained findings compared with patients' level of pain measured with the "VAS (Visual Analog Scale)" and the level of daily life activities measured by the "Neck Disability Index ".

Results: It was detected a statistically significant negative correlation between the VAS score and right vertebral artery diameter ($p=0.019$, $r=-0.518$). A significant reverse correlation between VAS score and right vertebral arterial blood flow rate ($p=0.011$, $r=-0.556$) was also observed. No correlation was found between other vertebral artery parameters and VAS score or Neck Disability Index ($p>0.05$).

Conclusion: The findings of this study revealed that there is a correlation between the vertebral artery flow rate and pain level. Clinicians must take into consideration vertebral pathologies in patients with neck pain because of this vital condition may accompany with various musculoskeletal pathologies such as cervical disc herniation.

Keywords: Vertebral artery, neck pain, disc herniation, cervical vertebrae.

INTRODUCTION

Cervical discogenic disorder is a major medical problem in the general population. The prevalence of the disease has increased with regard to age in both genders especially between the third and fifth decades (1,2).This clinical syndrome is characterized as a displacement of the nucleus pulposus in the intervertebral disc; as a result, the impingement of the cervical nerves may be formed at the exit section of the neural foramen or the compression of the spinal cord can be situated in the spinal canal (3).

Cervical discogenic pain, which is characterized by a stiffness or pain in neck movement, generally occurs as a result of disc degeneration (4). Symptoms are usually worsened by activities in which the neck is held in the same position for a long time such as working on a computer, reading, writing, driving, etc. (4). The pain caused by disc herniation is due to the disruption in the disc structure and the imbalance of the pressure distribution between the disc, vertebra endplate and facet joints (4). Such pain is mostly mechanical and local inflammation may also co-occur with the clinical condition (4). Besides the patients' symptoms, physical examination findings and magnetic resonance examination evidences also support the diagnosis.

The compressive forces caused by cervical disc herniation may also give rise to various degrees of microvascular damage by a venous obstruction that results in congestion

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and edema, which can lead to arterial ischemia (3). The circulation of the cervical spinal cord occurs mainly through the vertebral artery in which the development of circulatory findings or having circulatory diseases may increase the patient's complaints (5). Neck pain, ipsilateral arm pain, cervical paravertebral muscle spasm, restriction of cervical movement and paresthesias related to dermatomal dispersion are among the common symptoms of the cervical disc herniation that can lead to serious disabilities among patients (3,6). On the other hand; vascular pathologies of the cervical region, especially vertebrobasilar insufficiency, may give rise to similar findings in patients; it can also be detected simultaneously with cervical disc pathologies.

Vertebrobasilar insufficiency is a vascular pathology which is characterised by insufficient blood flow of the posterior circulation system supplied by two vertebral arteries that constituted the basillar artery (7). There are many risk factors including age, smoking, hypertension, hyperlipidemia that increase the likelihood of developing atherosclerosis for the vertebral artery insufficiency (7). This pathology can also lead to a number of neurological symptoms as vertigo, diplopia, dizziness, ataxia, headache, motor weakness in addition to neck pain (7). It may be the precursor of many pathologies such as medullary syndrome, posterior cerebral artery occlusion, cerebellar infarction, locked in syndrome (7) . Since vertebrobasilar insufficiency is a vital clinical condition and may exacerbate patients' clinical symptoms; it is essential to perform vascular examinations in patients with these symptoms.

There are many options in the treatment of cervical disc herniation including medications, physical therapy modalities, exercise practices and surgical treatment methods. However, some of the patients diagnosed with cervical disc herniation do not benefit from all of these treatments and it is observed that their complaints are ongoing. This situation has led us to investigate whether there are other underlying factors that may affect the level of pain in patients with cervical disc herniation. The most vital condition among these factors that shouldn't be ignored is the circulatory pathologies in the vertebral artery. In this study, it was aimed to investigate whether the circulatory properties of the vertebral arteries have an effect on the neck pain and functional status of the patients. To the best of our knowledge, this is the first study to evaluate the effect of vertebral artery parameters on cervical pain and disability in patients who were diagnosed with cervical disc herniation. By the results of this study, it was aimed to increase the awareness of clinicians on this issue. It was also intended to emphasize that in patients with a diagnosis of cervical disc herniation, the source of pain may not originate only from the musculoskeletal system.

MATERIAL AND METHOD

This prospective, observational study was performed at a tertiary hospital and intended to investigate the influence of vertebral artery characteristics on pain intensity and physical function between May 2018 and May 2019. All participants signed the informed consent form. This study was approved by Karabuk University Non-interventional Clinical Researchs Ethics Committee (Date: 02.05.2018, Decision No: 5/6). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The participants of the study were selected from patients diagnosed with cervical disc herniation as reflected in their medical history, physical examinations and magnetic resonance imaging (MRI) findings. The participants who experienced complaints such as dizziness, headaches, diplopia, blindness, imbalance, numbness, weakness and who had risk factors of hypertension, diabetes mellitus, hyperlipidemia, family history for cardiovascular diseases, smoking and obesity were included in the study. Vertebral artery and carotid artery doppler ultrasonography was performed in these patients, thus any stenosis or insufficiency in the vascular systems of the neck was evaluated. Moreover; vertebral blood flow rate (ml/min), vessel diameter (mm), minimum blood flow velocity (Vmin) and maximum blood flow velocity (Vmax) was measured by performing doppler ultrasonography. The patients' level of pain was measured by using a 100 mm Visual Analog Scale (VAS) score and the level of daily life activities was detected by the Neck Disability Index. These values were also compared according to the patients' demographic characteristics, comorbidities, body mass index values. It was investigated whether there was a significant difference between the specified values.

There are many clinical instruments available for assessing disability in cervical discogenic disorders. The Neck Disability Index, which is the first created scale for neck pain related disability, is the most commonly used self report instrument for evaluating status of neck pain related disability in clinical researches (8-11). The instrument is a disease-specific scale for assessing pain intensity, personal care, headaches, concentration, sleeping, recreation, lifting ability and neck pain induced by reading, working and driving (12).

Based on the participants' medical history, physical examination, and radiological examination, sixty five patients were diagnosed with cervical disc herniation and twenty patients who met the inclusion criteria were included and completed the study. The inclusion criteria for the participants were as follows:

(1) Being 18 years old or older

(2) Being diagnosed with cervical disc herniation with no advanced herniation and no nerve compression at

the level of extrusion or sequestration in the current MRI in addition to incidences of neck pain

(3) Having one or more symptoms of vertebrobasilar insufficiency such as headache, nausea-vomiting, dizziness, diplopia, syncope, vision problems, balance problems, numbness and loss of strength

(4) Having one or more of the risk factors for circulatory disorders such as rheumatic disease, migraine, hypertension, cigarette addiction, obesity, atherosclerosis, history of embolism, artery dissection, coagulopathy, fibromuscular dysplasia and Takayasu arteritis

(5) Having no signs of stenosis or failure in the carotid artery doppler examination

(6) Having no history of trauma

(7) Being willing to participate in the study

On the other hand, the exclusion criteria were as follows:

(1) Having major general health problems (e.g., heart failure or chronic obstructive pulmonary disease), metabolic disorders, acute or chronic infectious disorder and malignancy

(2) Having pregnancy

(3) Refusing to participate in the study

The flow chart of the study is presented in **Figure 1.**

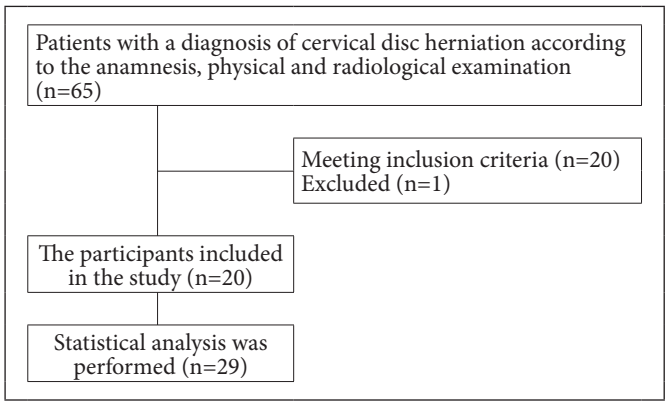

Figure 1. The Flow Chart of the Study

Statistical analyses were performed using the version 22.0 of SPSS software (IBM Corp., Armonk, NY, USA). The conformity of univariate data to normal distribution was evaluated by Kolmogorov-Smirnov test and Shapiro-Wilk Francia test; while variance homogeneity was evaluated with Levene test. Mann-Whitney U test and Exact results were used together in comparing two independent groups according to quantitative data. Spearman's rho test was applied to examine the correlations of variables. Bagging Linear Regression analysis was used to reveal the causality between the dependent variables (Visual Analog Scale and Neck Disability Scale) and other independent variables. Median value was determined as the coupling parameter. Information criterion (AICC) method in forward stepwise method was selected from the model selection methods. Neural Network (Multilayer Perceptron) as one of the consulting machine learning methods was used to find and estimate the most important independent variable with dependent variables (Visual Analog Scale and Neck Disability Scale). Gradient descent was selected for optimization algorithm. Hyperbolic tangent was applied for hidden layer activation function and identity was used for output layer activation function. Mini-Batch method was used for training data selection and calibrated as 70% vs 30% for training and testing sets respectively. Quantitative variables are determined as mean±SD (standard deviation) in tables and median (minimum/maximum); while categorical variables were shown as n (%). Variables were analyzed with a 95% confidence level and p value of less than 0.05 was considered as significant.

RESULTS

The mean age of the participants was 45.95±14.86 years. Majority of the participants were female with a ratio of 90 % (n=18) and 10% were male (n=2). The mean value of BMI was found to be 27.37±3.58. The duration of neck complaints was 10.45±1.49 months. The patient characteristics are presented in **Table 1** and **Table 2**.

Table 1. The characteristics of the participants

	Mean (SD.)	Median (Min/Max)
Age	45.95 (14.86)	43 (23/72)
BMI	27.38 (3.58)	28.65 (19/32.4)
	N	**%**
Gender		
Female	18	90.0%
Male	2	10.0%
Smoke		
No	18	90.0%
Yes	2	10.0%
Comorbidity		
No	6	30.0%
Yes	14	70.0%
Diabetes	3	15.0%
Asthma	2	10.0%
Hypertension	1	5.0%
Gastritis	1	5.0%
Hypothyroidism	1	5.0%
Diabetes+Gastritis	1	5.0%
Diabetes+Hypertension	2	10.0%
Asthma+Vertigo	1	5.0%
Hypothyroidism+Migraine	1	5.0%
Hypertension+Depression	1	5.0%

SD.: Standard deviation, n: Number of participants

Table 2. The complaints of the participants

Patient complaints	n	%
Neck pain+Numbness in upper extremity	10	50.0%
Neck pain+Numbness in upper extremity+Dizziness	2	10.0%
Neck pain+Dizziness+Headache	2	10.0%
Neck pain+Dizziness	2	10.0%
Neck pain+Loss of strength in upper extremity	1	5.0%
Neck pain+Numbness in upper extremity+Double Vision	1	5.0%
Neck pain+Earache+Dizziness	1	5.0%
Neck pain+Headache	1	5.0%

n: Number of participants

The vertebral artery characteristics of the patients were also analyzed. Vessel differentiation was also observed along with the bilateral vertebral arteries' diameter, minimum blood flow velocity (Vmin), maximum blood flow velocity (Vmax) and blood flow rate (ml/min). The mean values of the vessel diameters of the right and left arteries were 4.89±7.1 and 4.2±5.8 respectively. The mean blood flow rates of the right and left vertebral arteries were 2.60±0.46 and 2.89±0.32 respectively. The mean values of the Vmax and Vmin of the right vertebral artery were 39.40±16.29 and 11.10±3.58 whereas that of the left vertebral artery were 42.25±12.83 and 14.0±6.03 respectively. The vertebral artery characteristics of the participants are presented in **Table 3**.

Table 3. The vertebral artery characteristics of the participants

	Right Vertebral Artery Mean (SD.)	Left Vertebral Artery Mean (SD.)
Vessel Diameter (mm)	4.89±7.1	4.2±5.8
Minimum Blood Flow Velocity (Vmin)	11.1±3.6	42.25±12.83
Maximum Blood Flow Velocity (Vmax)	39.4±16.2	14.0±6.03
Blood Flow Rate (ml/min)	78.5±44.4	101.0±42.3

SD.: Standard Deviation

Based on the analysis of the pain and neck disability levels, it was shown that the mean value of VAS scores was 36.25±32.5 and that of the Neck Disability Index scores was 16.6±5.78. It was detected a statistically significant negative correlation between the VAS score and right vertebral artery diameter (p= 0.019, r=-0.518). A significant reverse correlation between the VAS score and right vertebral arterial blood flow rate (p=0.011, r=-0.556) was also observed (**Figure 2** and **Figure 3**). No correlation was found between other vertebral artery parameters and VAS score (p > 0.05). Furthermore, no correlation between the Neck Disability Index scores and vertebral artery characteristics was found (p > 0.05) (**Table 4**).

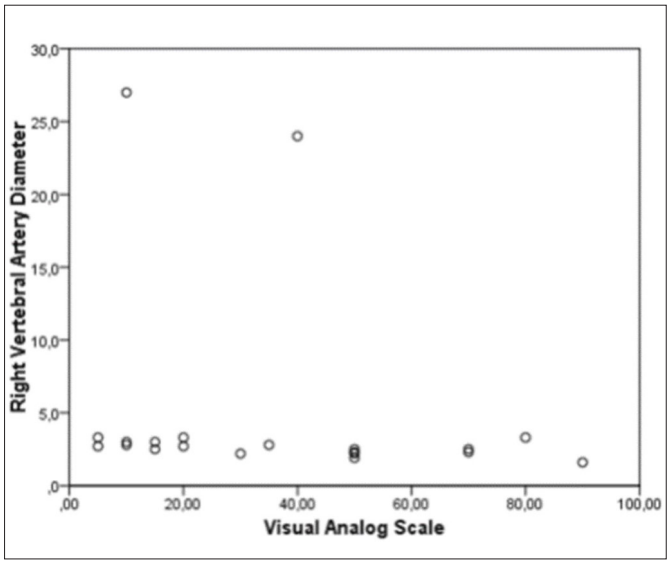

Figure 2. The Correlation between Right Vertebral Artery Diameter (mm) and VAS Level

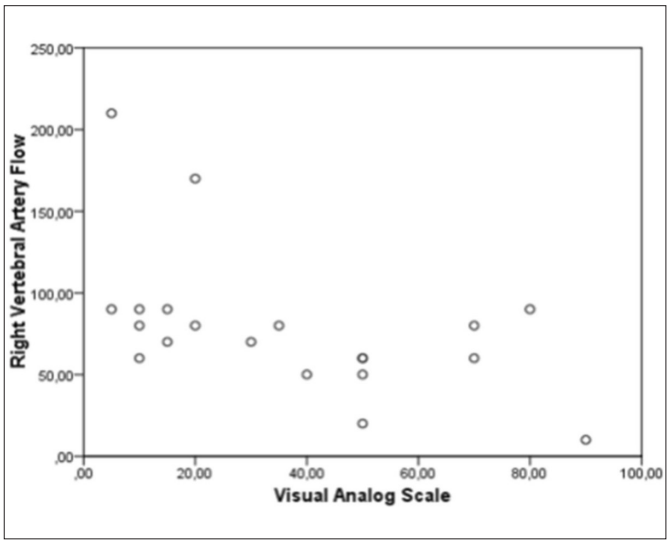

Figure 3. The Correlation between Right Vertebral Artery Flow Rate (ml/min) and VAS **Level**

Table 4. The Correlation table of the study findings (Spearman's rho Test)

	Neck Disability Scale		Visual Analog Scale	
	r	p	r	P
Age	-0.240	0.307	-0.165	0.487
BMI	0.190	0.422	0.184	0.438
Right Vertebral Artery Diameter	0.449	0.050	-0.518	0.019
Right Vertebral Artery Flow	0.318	0.172	-0.556	0.011
Right Vertebral Artery Vmax	0.051	0.831	-0.188	0.427
Right Vertebral Artery Vmin	0.144	0.546	-0.304	0.192
Left Vertebral Artery Diameter	-0.244	0.299	0.268	0.253
Left Vertebral Artery Flow	-0.372	0.106	0.110	0.644
Left Vertebral Artery Vmax	-0.254	0.280	0.073	0.759
Left Vertebral Artery Vmin	-0.241	0.307	-0.197	0.404
Total Vertebral Artery Flow Rate	0.085	0.723	-0.258	0.271

r: correlation coefficient, p: probability value (p value)

According to the Neural Network (Multilayer Perceptron) analysis, which is used to estimate the effects of variables on the Visual Analog Scale; the significance rates of the variables were 12.5% for right vertebral artery Vmin, 11.4% for left vertebral artery Vmax ,10.5% for duration of pain (months), 10.1% for right vertebral artery Vmax, 9.3% for right vertebral artery flow, 7.8% for left vertebral artery Vmin, 7.0% for right vertebral artery diameter, 6.3% for total vertebral artery flow rate, 5.4% for comorbidity, 4.4% for left vertebral artery flow, 3.3% for smoke, 2.8% for left vertebral artery diameter, 2.6% for age, 2.6% for BMI, 2.5% for family history and 1.4% for gender variables. The prediction success of the model was calculated as 99.9% (**Table 5**).

Table 5. Significance ratios of variables on the Visual Analogue Scale and Neck Disability Index

	Visual Analog Scale (D.V.)	Neck Disability Scale (D.V.)
Independent Variable	**Importance**	**Importance**
Gender	1.4%	0.8%
Smoke	3.3%	5.1%
Comorbidity	5.4%	2.0%
Family History	2.5%	1.5%
Age	2.6%	6.2%
BMI	2.6%	8.2%
Right Vertebral Artery Diameter	7.0%	11.4%
Right Vertebral Artery Flow	9.3%	12.1%
Right Vertebral Artery Vmax	10.1%	5.7%
Right Vertebral Artery Vmin	12.5%	4.4%
Left Vertebral Artery Diameter	2.8%	11.1%
Left Vertebral Artery Flow	4.4%	12.5%
Left Vertebral Artery Vmax	11.4%	3.5%
Left Vertebral Artery Vmin	7.8%	6.3%
Total Vertebral Artery Flow Rate	6.3%	3.1%
Duration of pain (months)	10.5%	6.1%
n (%) : Training/Testing	20(100)/0(0)	20(100)/0(0)
Percentage of correct predictions: Training/Testing	99.9	99.9

Neural Network (Multilayer Perceptron), Hidden layer activation function: Hyperbolic tangent, Output layer activaction function: identity, DV: Dependent Variable

DISCUSSION

In the pathophysiology of cervical disc herniation; a clinical formation occurs as a result of the progression of the nucleus pulposus inside or under the posterior longitudinal structures due to the rupture of annulus fibrosus (13). On the other hand, the neck is an important area because of the large number of vessels and nerves in the vertebral column (14). Thus, additional pathologies can contribute to the severity of neck pain in patients with cervical disc herniation; thus vascular pathologies are of primary importance under these conditions. Vertebrobasilar insufficiency, which is one of these vascular problems, is a serious medical condition that should not be ignored in diagnosis.

Vertebral arteries allow the distribution of essential nutrition to the cervical spinal cord, making it the first and largest branch of the subclavian artery (5,15,16). They are located on both sides of the posterior neck and form the basillary artery at the base of the skull by circulating in the neural foramens between the first and seventh cervical vertebrae (17). The normal value of the total volume in bilateral vertebral arteries is over 200 ml/min and the decreased blood flow rate (less than 200 ml/min) is an indicator of vertebrobasilar failure (17). Atherosclerosis, embolism, arterial dissection, coagulopathies, fibromuscular dysplasia, migraine and substance abuse are among the causes of vertebrobasilar insufficiency; additionally, hypertension, cigarette addiction, and obesity are thought to be the main risk factors (18-20).

Many studies in the literature show that ischemic pathologies give rise to pain in the musculoskeletal system (21-26). These studies have shown that the amount of oxygen supplying the metabolic needs of the surrounding tissues is not provided adequately as a result of the decrease in blood flow in the skeletal muscle (21,27-33). It is also hypothesized that the obstruction of perfusion is the main reason for the pain experienced by the patients (21,32,34,35). In a review by Queme et al. it was also revealed that factors relating to the up-regulation of growth factors and cytokines within the muscles during ischemic conditions and microvascular changes may be linked to the over-expression of different receptor molecules in the dorsal root ganglia which will in turn modulate pain and sympathetic reflexes as observed in the recent evidences (21). It is suggested that the afferent sensitization due to ischemia is related with the interplay between the transient receptor potential channels, acid sensing ion channels, and purinergic (P2X and P2Y) receptors in sensory neurons (21,36).

There was a female predominance in our study which was in accordance with literature. In a study by Gaigalaite et al. it was revealed that vertebral artery hypoplasia was more common in women (33 %) rather than in men (23.5 %) and vertebral artery was found to be wider in males than in females (37). Similarly, the findings of another study by Schievink et al. which determines the long term follow up of patients with spontaneous recurrent cervical artery dissections showed that most of the patients with dissections of both vertebral artery and internal carotid artery were women (85%)(38). Singuim et al. also specified that the risk of vascular disease increases during menopause as a result of the decrease in endogenous estrogens, which reduces the risk of serious vascular events in their study (39). Additionally, they stated that the development of hypertension and diabetes during pregnancy will give rise to an increase for the risk of vascular disease in the future periods of their life (39).

To the best of our knowledge, this is the first study that investigates the influence of vertebral artery parameters on cervical pain and disability. In this study, it has found a significant reverse correlation between the right vertebral artery flow rate and VAS level. However, any correspondence between the left vertebral artery characteristics and VAS level wasn't found in our study. This could be due to the mean flow rate of the right vertebral artery being below the normal value of 100 ml/min; while the mean flow rate of the left vertebral artery is above the normal value of 100 ml/min. We hypothesized that the left vertebral artery, which has a normal mean value of blood flow rate, does not affect pain formation as it contributes to the adequate blood supply of the musculoskeletal structures on the left side of the neck. On the other hand, more clinical studies are needed to generalize the results obtained from this study.

While the present study achieved its intended objectives, limitations were also considered in terms of the small number of participants due to the application of the comprehensive inclusion criteria and territorial limits which includes the generalizability of these findings to other ethnic groups. However, this study can guide future studies because of the findings were able to present the clinical data and the direct complaints of the participants.

CONCLUSION

Overall, the findings of this study revealed a correlation between the vertebral artery flow rate, diameter and pain level. Vertebral artery pathologies are serious clinical conditions and a delay in diagnosis may cause a detrimental impact on the patients' vital functions. Clinicians must take into consideration vertebral pathologies in patients with neck pain, wherefore this vital condition has a tendency to co-occur with various musculoskeletal pathologies, such as cervical disc herniation.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Karabük University Non-interventional Clinical Researchs Ethics Committee (Date: 02.05.2018, Decision No:5/6).

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.

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REFERENCES

1. Kolenkiewicz M, Włodarczyk A, Wojtkiewicz J. Diagnosis and incidence of spondylosis and cervical disc disorders in the university clinical hospital in Olsztyn, in years 2011-2015. Biomed Res Int 2018; 2018: 1-7.
2. Kim YK, Kang D, Lee I, Kim SY. Differences in the incidence of symptomatic cervical and lumbar disc herniation according to age, sex and national health insurance eligibility: A pilot study on the disease's association with work. Int J Environ Res Public Health 2018; 15: 1-9.
3. Sharrak S, Al Khalili Y. Cervical Disc Herniation. StatPearls [Internet] 2020 (access date: 18 Jun 2021). Available from: https://www.ncbi.nlm.nih.gov/books/NBK546618/.
4. Isaac Z, Kelly HR. Evaluation of the adult patient with neck pain. UpToDate [Internet]. 2014 (access date: 18 Jun 2021). Available from: https://www.uptodate.com/contents/evaluation-of-the-adult-patient-with-neck-pain.
5. Günaydın Ş, Çağlar N, Tütün Ş, Çetin E, Özgönenel L, Altın F. Servikal disk hernisine bağlı kronik boyun ağrısında elektroakupunktur ve TENS karşılaştırılması. İstanbul Tıp Derg 2010; 11: 104-8.
6. Binder AI. Cervical spondylosis and neck pain. BMJ 2007; 334: 527-31.
7. Pirau L, Lui F. Vertebrobasilar Insufficiency. In: StatPearls. Treasure Island (FL): StatPearls Publishing; March 24, 2021
8. Pietrobon R, Coeytaux RR, Carey TS, Richardson WJ, DeVellis RF. Standard scales for measurement of functional outcome for cervical pain or dysfunction: a systematic review. Spine 2002; 27: 515-22.
9. Resnick DN. Subjective outcome assessments for cervical spine pathology: A narrative review. Journal of Chiropractic Medicine 2005; 4: 113-34.
10. MacDermid JC, Walton DM, Avery S, et al. Measurement properties of the neck disability index: a systematic review. J Orthop Sports Phys Ther 2009; 39: 400-17.
11. Kesiktas N, Ozcan E, Vernon H. Clinimetric properties of the Turkish translation of a modified neck disability index. BMC Musculoskelet Disord 2012; 13: 25.
12. Vernon H. The neck disability index: state-of-the-art, 1991-2008. J Manipulative Physiol Ther 2008; 31: 491-502.
13. Kızıl R. Sservikal disk hernileri. Turkiye Klinikleri J PM&R-Special Topics 2009; 2: 35-43.
14. Aksakallı E, Turan Y. Boynun fonksiyonel anatomisi ve değerlendirmesi. Turkiye Klinikleri J PM&R-Special Topics 2009; 2: 1-10.
15. Fielding JW, Hensinger RN. Cervical spine surgery: past, present, and future potential. Orthopedics 1987; 10: 1701-5.
16. Russell EJ, D'Angelo CM, Zimmerman RD, Czervionke LF, Huckman MS. Cervical disk herniation: CT demonstration after contrast enhancement. Radiology 1984; 152: 703-12.
17. Yurdakul S, Aytekin S. Doppler ultrasound imaging of the carotid and vertebral arteries. Turk Kardiyol Dern Ars 2011; 39: 508-17.

18. Lima Neto AC, Bittar R, Gattas GS, et al. Pathophysiology and diagnosis of vertebrobasilar insufficiency: A review of the literature. International archives of otorhinolaryngology 2017; 21: 302-7.
19. Savitz SI, Caplan LR. Vertebrobasilar disease. N Engl J Med 2005; 352: 2618-26.
20. Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. Neurology 1989; 39: 1246-50.
21. Queme LF, Ross JL, Jankowski MP. Peripheral mechanisms of ischemic myalgia. Front Cell Neurosci 2017; 11: 419.
22. Alam M, Smirk FH. Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. J Physiol 1937; 89: 372-83.
23. Sinoway L, Prophet S, Gorman I, et al. Muscle acidosis during static exercise is associated with calf vasoconstriction. J Appl Physiol 1989; 66: 429-36.
24. Coderre TJ, Xanthos DN, Francis L, Bennett GJ. Chronic post-ischemia pain: A novel animal model of complex regional pain syndrome-type I produced by prolonged hindpaw ischemia and reperfusion in the rat. Pain 2004; 112: 94-105.
25. Laferrière A, Millecamps M, Xanthos DN, et al. Cutaneous tactile allodynia associated with microvascular dysfunction in muscle. Mol Pain 2008; 4: 49.
26. Ross JL, Queme LF, Shank AT, Hudgins RC, Jankowski MP. Sensitization of group III and IV muscle afferents in the mouse after ischemia and reperfusion injury. J Pain 2014; 15: 1257-70.
27. Dennis GJ, Keating RM. Muscle infarction in sickle cell anemia. Ann Intern Med 1991; 115: 831-2.
28. Norris SL, Gober JR, Haywood LJ, et al. Altered muscle metabolism shown by magnetic resonance spectroscopy in sickle cell disease with leg ulcers. Magn Reson Imaging 1993; 11: 119-23.
29. Kasikcioglu E, Dinler M, Berker E. Reduced tolerance of exercise in fibromyalgia may be a consequence of impaired microcirculation initiated by deficient action of nitric oxide. Med Hypotheses 2006; 66: 950-52.
30. Katz DL, Greene L, Ali A, Faridi Z. The pain of fibromyalgia syndrome is due to muscle hypoperfusion induced by regional vasomotor dysregulation. Med Hypotheses 2007; 69: 517-25.
31. Nishida Y, Saito Y, Yokota T, Kanda T, Mizusawa H. Skeletal muscle MRI in complex regional pain syndrome. Intern Med 2009; 48: 209-12.
32. Coderre TJ, Bennett GJ. A hypothesis for the cause of complex regional pain syndrome-type I (reflex sympathetic dystrophy): Pain due to deep-tissue microvascular pathology. Pain Med 2010; 11: 1224-38.
33. McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. Circ Res 2015; 116: 1540-50.
34. Elvin A, Siösteen AK, Nilsson A, Kosek E. Decreased muscle blood flow in fibromyalgia patients during standardised muscle exercise: a contrast media enhanced colour Doppler study. Eur J Pain 2006; 10: 137-44.
35. Chalaye P, Lafrenaye S, Goffaux P, Marchand S. The role of cardiovascular activity in fibromyalgia and conditioned pain modulation. Pain 2014; 155: 1064-69.
36. Gibbons DD, Kutschke WJ, Weiss RM, Benson CJ. Heart failure induces changes in acid-sensing ion channels in sensory neurons innervating skeletal muscle. J Physiol 2015; 593: 4575-87.
37. Gaigalaite V, Vilimas A, Ozeraitiene V, et al. Association between vertebral artery hypoplasia and posterior circulation stroke. BMC Neurol 2016; 16: 118.
38. Schievink WI, Mokri B, O'Fallon WM. Recurrent spontaneous cervical-artery dissection. N Engl J Med 1994; 330: 393-97.
39. Singium AN, Vesin C, Safar M, Blacher J. Vascular risk factors in women. Sang Thrombose Vaisseaux 2009; 21: 63-70.

Original Article

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Investigation of the patients' perception on dental treatment and their anxiety levels during the COVID-19 pandemic process

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ABSTRACT

Aim: The objectives of this study are to evaluate the anxiety levels of patients toward dental treatment during the pandemic process, to obtain information about the level of awareness, perceptions and attitudes of patients seeking dental treatment and to determine the relationship between anxiety levels and socio-demographic variables of individuals.

Material and Method: A total of 300 patients who applied to the dentistry faculty were included in the study, and a survey questionnaire was administered to these patients. The survey consisted of three parts; in the first part, the socio-demographic features of the patients were asked, in the second, the State-Trait Anxiety Inventory (STAI) developed by Spielberger was used to measure the level of anxiety, and in the last part, a questionnaire form about the perceived sensitivity to COVID-19 developed by the authors was applied. The statistical analysis of the data was performed with SPSS for Windows version 24.0 and a p value less than 0.05 was accepted as statistically significant. The normality of distribution of continuous variables was tested by the Shaphiro-Wilk test. The Mann Whitney U, Kruskal-Wallis and Dunn multiple comparison tests were used to compare non-normal data between two or more groups.

Results: A total of 300 patients, 155 men and 145 women, participated in the study. The mean state anxiety score was 43.38±8.34. Significant differences were not found among the independent variables affecting the level of anxiety, age, gender, marital status, education, whether individuals have had COVID-19. When the questions evaluating the patients' perception on dental treatment were compared with the anxiety scores, there were statistically significant differences among groups.

Conclusion: The study results revealed that the patients had a high level of anxiety in places such as dental hospitals where many patients are treated, but they were aware of the preventive measures to be taken during the pandemic process.

Keywords: COVID-19, dental treatment, anxiety

INTRODUCTION

COVID-19 is a viral infection caused by the new type of corona virus that emerged in Wuhan, China, in 2019. The disease then spread to the rest of Asia, Europe, America and the whole world and was declared as a "pandemic" by the World Health Organization (WHO) on March 11, 2020. COVID-19 is highly contagious and transmitted directly through coughing, sneezing or indirectly through person-to-person contact and saliva. It has also been reported that the COVID-19 virus can be transmitted by aerosols formed during medical and dental procedures (1). There is a high risk of cross infection between dentists and patients in dental clinics and hospitals. Since dentists work in close proximity with patients, they are at particularly high risk of being infected by, as well as transmitting COVID-19 to, their patients (2). In order to prevent the spread of the disease, individuals are constantly informed about wearing masks, maintaining social distance, and complying with hygiene rules. However, achieving success in the pandemic process depends on the awareness and attitude of the individuals. At the onset of the pandemic, only emergency dental treatments were allowed in many countries, in line with the recommendations of National Dental Councils. However, with the normalization, when dentists take all protective measures, they can also perform routine dental treatments (3). Various protective precautions are taken especially in dentistry faculties or hospitals where many patients are treated. These precautions include the use of protective equipment, deep ventilation filtering,

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increased attention to complying with personal hygiene behaviors, ensuring social distance among patients and vaccination of doctors and healthcare professionals in the hospital. Dentists started to treat patients by taking all necessarry precautions, but the thought that there is a risk of contamination while receiving dental treatment in patients continues. Especially in dentistry faculties or hospitals, patients avoid seeking dental treatment.

Another problem seen in the pandemic process is psychological health of individuals. The pandemic has brought some concerns and anxiety in people. The anxiety is defined as extensive emotional reaction emerging against dangerous situations or events, aimed at adapting to current conditions (4). Two types of anxiety are defined as "state anxiety" and "trait anxiety". State anxiety is defined as a temporary emotional state characterized by subjective feelings of tension and fear. Trait anxiety, on the other hand, shows the anxiety tendency that exists in the individual relatively, and it is the state of intensification and continuity of state anxiety (4,5). Various scales have been developed to measure anxiety in people. The State-Trait Anxiety Inventory (STAI) was developed by Speilberger et al. to measure state and trait anxiety (5).

During the pandemic process, some people developed psychological problems due to the quarantine, while some others experienced high anxiety. Despite the great importance given to the measures taken regarding the pandemic, determining the mental health of people affected by the pandemic has been relatively neglected. Being aware of the anxiety and perception of individuals that may arise during the pandemic is important in terms of the spread and control of the disease. There are many studies in the literature examining the anxiety levels of dentists against COVID-19, and most of them have shown that treating patients with protective equipment is not seen as a problem for dentists (2,3,14). However, studies conducted with patients are not sufficient, thus one of the aims of this study is to measure the state anxiety levels of patients who apply for dental treatment. Compared to period when the pandemic first started, many patients, felt safe in the face of the measures taken and began to receive dental treatment. Another purpose of the study is to determine how the protective measures taken were perceived by patients and their reactions against protective measures while being treated. For these purposes, the following questions were answered in this study:

- Is there a significant difference between the state anxiety levels and socio-demographic characteristics of the participants?
- Is there a significant difference between the state anxiety levels of paticipants and patient-related questions?

MATERIAL AND METHOD

The survey was approved by the Gaziantep University Clinical Researchs Ethics Committee (Date: 10.03.2021, Decision No: 2021/68). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Since the number of individuals in the target audience was unknown, the total sample size was determined based on the percentage measurement values of the studies and calculated using the G-Power software with a confidence interval of 95% and a margin of error of 5%.

The cross-sectional study was conducted with 300 patients receiving dental treatment in the dentistry faculty of Gaziantep University. All the patients invited responded to the survey (100%). An interview survey was designed to collect the data and administered by two dentists. The survey consisted of three parts; in the first part socio-demographic variables of participants such as gender, age, education, marital status and if she/he had COVID-19 before were asked. The second part includes COVID-19 and patient-related questions prepared by two dentists. In the last part, Spielberger's STAI-S (state) anxiety scales were administered to the patients.

The anxiety level was measured using the State-Trait Anxiety Inventor developed by Spielberger et al., that consists of 40 items and two sub-inventories measuring the state and trait anxiety levels (5). The adaptation of the inventory to Turkish and validity-reliability study of the Turkish version were carried out by Oner and Le Compte (6). In this study, only the State Anxiety subscale was used. The reason for this is that the State Anxiety Scale describes how the individual feels at a certain time and under stressful conditions and includes the response by taking into account individuals' feelings about the current situation. The state Anxiety Scale consists of 20 items in total. There is no time limit for answering the scale consisting of short statements. Emotions or behaviors expressed in the items of State Anxiety Scale are answered by marking one of the options as (1) none, (2) some, (3) much, (4) completely, according to their severity. There are two types of expressions in the scale as called direct/straight and inverted expressions. Direct statements express negative emotions, while inverted statements express positive feelings. Answers with a value of 4 in direct expressions indicate that the anxiety is high. On the other hand, in inverted expressions, answers with a value of 1 refer high anxiety, a score of 4 indicates low anxiety.

The SPSS 24.0 software for windows was used for the statistical analysis of the data. While evaluating the study data, in addition to using descriptive statistical methods (mean, standard deviation, median, frequency, ratio,

minimum, maximum), the conformity of the data to normal distribution was checked with the Shaphiro-Wilk test. The Mann-Whitney U, Kruskal Wallis and Dunn multiple comparison tests were used to compare non-normal data between 2 or more groups. The significance was evaluated at p<0.05 level.

RESULTS

A total of 155 men (51.7%) and 145 women (48.3%) participated in the study. Of the patients included in the study, 159 (53%) were between the ages of 18 and 38, 95 (31.7%) were between the ages of 39 and 59, and 46 (15.3%) were between the ages of 60 and 80. It was determined that 68 participants (22.7%) were elementary school graduates, 35 (11.7%) were secondary school graduates, 82 (27.3%) were high school graduates and 115 (38.3%) were university graduates. There were 163 (54.3%) married patients and, 132 (45.7%) single patients. It was found that 63 patients (21%) had COVID-19, 237 (79%) did not have (**Table 1**).

The mean state anxiety score of the patients included in the study was found to be 43.38±8.34. The relationship between the state anxiety score and the demographic data was examined. When the relation of state anxiety score according to age was evaluated, it was determined that there was no statistically significant difference among all age groups. Considering the mean state anxiety scores in terms of gender, the anxiety scores of women were higher, but there was no statistically significant difference between the genders. There was no statistically significant effect of marital status and educational status on the mean state anxiety score. Although the mean anxiety score of those who had COVID-19 was slightly higher, there was no statistically significant difference in terms of the state anxiety score between the patients who had COVID-19 and those who did not have (**Table 2**).

The frequency data of the answers given to the COVID-19 and patient-related questionnaire form, which constitutes the last part of the survey, are summarized in **Table 3**. Comparing the mean state anxiety score by patient-related questions, it was found that the mean state anxiety scores were statistically significantly different among the answers to the questions (**Table 4**). The anxiety score of those who think that COVID-19 can be transmitted through dental treatment was statistically significantly higher than those who think that otherwise (p<0.001). The scores of those who said no were found to be significantly lower than the hesitant (p<0.041). The anxiety score of those who thought that adequate measures were taken in the dental unit was found to be significantly lower than those who said both no and hesitant (p<0.001, p<0.001, respectively). The anxiety score of those who found the measures taken by dentists sufficient while treating the patient was found to be statistically significantly lower than those who found insufficient and hesitant (p<0.001). The anxiety score of the patient who said no to the question of whether they would seek dental treatment if their condition was not urgent was found to be statistically significantly higher than those who said yes (p<0.003). The anxiety score of those who said yes to the question of whether they think dentist clinics have a high risk of contamination was found to be statistically

Table 1. Demographic features of the patients

	Descriptive features (n=300)	
	Mean±SD	**Median (Min-Max)**
STAI(Anxiety) scores	43.38±8.34	44 (20 -76)
	n	**%**
Age		
18-38	159	53.0
39-59	95	31.7
60-80	46	15.3
Gender		
Female	145	48.3
Male	155	51.7
Education		
Elemantary school	68	22.7
Secondary school	35	11.7
High school	82	27.3
University+Graduate degree	115	38.3
Marital status		
Married	163	54.3
Single	137	45.7
Had COVID-19 infection		
Yes	63	21.0
No	237	79.0

Table 2. Associating the STAI scale scores with the demographic features

Variables	n	Mean±SD	p
Age			0.318
18-33	159	43.08±8.61	
39-59	95	43.96±8.44	
60-80	46	43.26±7.18	
Gender			0.083
Female	145	44.54±7.64	
Male	155	42.3±8.82	
Education			0.897
Elemantary school	68	43.57±7.72	
Secondary school	35	42.86±9.16	
High school	82	43.5±7.89	
University+Post graduate	115	43.35±8.82	
Marital status			0.258
Married	163	43.72±8.67	
Single	137	42.99±7.94	
Had COVID-19 infection			0.118
No	237	43.12±8.35	
Yes	63	44.37±8.29	

*Significant at 0.05 level; Mann Whitney U test for 2 groups, Kruskal Wallis test for 3 or more groups

significantly higher than those who said no (p<0.011). The anxiety score of the patients who thought that the dentist can transmit COVID-19 during dental treatment was found to be statistically significantly higher than those who thought otherwise (p<0.013). The anxiety score of those who said yes to the question of whether they think they could be infected with COVID-19 from the other patients in the waiting area was statistically significantly higher than those who said no (p<0.010). The anxiety score of those who said yes to the question of whether they feel safe because healthcare professionals received the COVID-19 vaccine was found to be statistically significantly lower than those who said no (p<0.004). There was no statistically significant difference between the anxiety scores of those who said yes, no and hesitant to the question of whether they would like to be vaccinated if they have the option.

The anxiety score of those who said yes to the question of whether they would have had your dental treatment safely if vaccinated, was found to be statistically significantly lower than those who said both no and hesitant (p<0.001, p<0.003, respectively).

Table 3. Answers given to the COVID-19 and patient-related questionnaire form

		n	%
1-Do you think COVID-19 can be transmitted by receiving dental treatment?	Yes	127	42.3
	No	107	35.7
	Hesitant	66	22.0
2-Do you think that adequate measures are taken in the unit you apply for a dental treatment?	Yes	246	82.0
	No	25	8.3
	Hesitant	29	9.7
3-Do you find the measures taken by dentists sufficient? (Disposable gowns, masks, visors, caps, etc.)	Yes	268	89.3
	No	14	4.7
	Hesitant	18	6.0
4-If your situation was not urgent, would you apply for dental treatment?	Yes	75	25.0
	No	192	64.0
	Hesitant	33	11.0
5-Do you think dental clinics have a high risk of contamination?	Yes	133	44.3
	No	109	36.3
	Hesitant	58	19.3
6-Do you think you can get COVID-19 from your dentist during dental treatment?	Yes	94	31.3
	No	156	52.0
	Hesitant	50	16.7
7-Do you think you can get COVID-19 from other patients in the waiting room?	Yes	178	59.3
	No	78	26.0
	Hesitant	44	14.7
8-Do you feel safe because healthcare professionals receive COVID-19 vaccine?	Yes	206	68.7
	No	51	17.0
	Hesitant	43	14.3
9-If you have the option of vaccination, would you like to have it?	Yes	202	67.3
	No	61	20.3
	Hesitant	37	12.3
10-If you were vaccinated, would you have your dental treatment safely?	Yes	204	68.0
	No	40	13.3
	Hesitant	56	18.7

DISCUSSION

The rapid spread of COVID-19 around the world has caused significant healthcare problems. In addition to the fact that the pandemic process physically affects people, many psychological problems have also occurred. It has traumatic effect on humans and causes their anxiety levels to increase (7). Especially during the dental treatment, it has been reported that there is a serious risk of contamination for dentists, dental staff and patients (1,8,9). Therefore, the purpose of this study is to evaluate the dental anxiety level of patients during the COVID-19 pandemic process and to obtain information about the level of awareness, perceptions and attitudes of patients seeking dental treatment.

Table 4. The relationship between the STAI scale scores and the survey questions

Questions	n	Mean±SD	p
QUESTION 1			0.001*
Yes	127	45.35±7.11	
No	107	40.97±8.93	
Hesitant	66	43.5±8.63	
QUESTION 2			0.001*
Yes	246	42.35±8.17	
No	25	48.76±8.89	
Hesitant	29	47.55±6.05	
QUESTION 3			0.001*
Yes	268	42.73±8.13	
No	14	48.07±10.75	
Hesitant	18	49.5±5.54	
QUESTION 4			0.007*
Yes	75	40.57±9.36	
No	192	44.69±7.54	
Hesitant	33	42.15±8.79	
QUESTION 5			0.034*
Yes	133	45.05±7.27	
No	109	41.51±9.13	
Hesitant	58	43.07±8.43	
QUESTION 6			0.039*
Yes	94	45.19±6.88	
No	156	42.19±8.98	
Hesitant	50	43.7±8.26	
QUESTION 7			0.019*
Yes	178	44.72±7.44	
No	78	41.42±8.98	
Hesitant	44	41.43±9.63	
QUESTION 8			0.012*
Yes	206	42.41±8.68	
No	51	46.22±8.14	
Hesitant	43	44.67±5.69	
QUESTION 9			0.129
Yes	202	43.29±8.57	
No	61	42.39±7.93	
Hesitant	37	45.54±7.51	
QUESTION 10			0.001*
Yes	204	42.11±8.51	
No	40	46.55±8.41	
Hesitant	56	45.75±6.43	

*Significant at 0.05 level; Kruskal-Wallis test.

When the results obtained in the study were examined, no difference was detected between the socio-demographic data of the individuals and their state anxiety scores. In many studies, it has been found that women perceive the disease as more contagious and lethal, and experience higher levels of anxiety (10,11). Also the studies conducted during the COVID 19 pandemic revealed that women experience higher levels of anxiety than men (12,13). In the present study, no difference was determined in terms of anxiety levels between men and women. These results are similar to the result of a study reporting that women and men were psychologically affected by the pandemic at the same level of stress and anxiety (14).

In the present study, no statistically significant difference was found between the state anxiety level scores according to the age variable. Similar to our results, a previous study indicated that there was no statistically significant difference between the state anxiety level scores and age variable, however, it was reported that there was a statistically significant difference in the trait anxiety level scores according to the age variable (13). There are many studies reporting that anxiety level is not affected by age (15,16). However, it has been determined that the anxiety levels of young people were higher in studies conducted during the COVID-19 pandemic process (17,18,19). It was found in the study that the anxiety score of those who had COVID 19 was higher. Given the difficulties experienced by individuals with the disease, it is considered normal to have higher levels of anxiety. Shevlin et al. (17) stated that being married and having children increased the stress level during the COVID-19 pandemic. However, in the present study, no significant difference was detected between married and single participants in terms of the mean state anxiety scores.

The data we obtained in the study revealed that the majority of individuals think that they can be infected with COVID-19 by receiving dental treatment. Sahin et al. (20) reported similar results in their study. In addition, in the present study and other studies, it has been indicated that patients would consult a dentist in only emergency cases during the pandemic process (21). Therefore, the precautions taken in dental clinics are very important in terms of patients' perspective on dental treatment. During the pandemic process, in dental clinics; the importance given to personal protective equipment has been increased, the use of equipment such as disposable protective clothing, disposable cap, protective glasses, face shield, N95 mask has been increased. Disinfection points have been created in common areas for hand hygiene, essential measures have been taken for maintaining social distance, and in particular, dentistry applications causing aerosol formation have been provided in rooms that are adequately ventilated with natural air flow. In the present study, the majority of patients thought that the precautions taken in dental clinics were sufficient, and when the anxiety score of the individuals was evaluated, it was observed that the anxiety scores of those who thought that adequate precautions were taken were lower.

It was found in the study that the number of people who thought that they can get COVID-19 from the dentist during dental treatment was less than those who thought that they would not be infected. On the other hand, the number of those who thought that other patients can transmit COVID-19 in the waiting area was more than those who thought otherwise. Similar to these results, Moffat et al. reported that the greatest risk related to dental care in terms of COVID-19 was to contract the disease from other patients in the dental office (22). These data indicate that the precautions taken by dentists while treating patients instill confidence in patients.

At the time of this study, almost all healthcare professionals were vaccinated against COVID-19, but the majority of patients had not yet been vaccinated. As a result of the survey, it could be said that the vast majority of patients feel safe because healthcare professionals have been vaccinated. At the same time, the majority of patients stated that if there was an option, they would want to be vaccinated. In addition, according to the results of the study, the number of people who think that they can receive dental treatment safely if they are vaccinated is quite high.

CONCLUSION

It has been observed that the anxiety level of patients who applied to dental clinics for dental treatment have increased during the COVID-19 pandemic process. However, the measures taken in this process increase confidence in the patients. The present study demonstrated that patients were aware of the recommendations related to COVID-19 disease and the importance of being vaccinated and concluded that being vaccinated reduce the anxiety level of people. It is recommended to carry out similar studies on larger populations to obtain comprehensive and comparable data.

ETHICAL DECLARATIONS

Ethics Committee Approval: The survey was approved by the Gaziantep University Clinical Researchs Ethics Committee (Date: 10.03.2021, Decision No: 2021/68).

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. Peker İ, Pamukçu U, Taka K, Üçok Ö. Diş hekimliği pratiğinde Koronavirüs salgınına karşı alınması gereken önlemler. Turkiye Klinikleri J Dental Sci 2021; 27: 294-306
2. Meng L, Hua F, Bian Z. Coronavirus disease 2019 (COVID-19): Emerging and future challenges for dental and oral medicine. J Dent Res 2020; 99: 481–7.
3. Khader Y, Al Nsour M, Al-Batayneh OB, et al. Dentists' awareness, perception, and attitude regarding COVID-19 and infection control: cross-sectional study among Jordanian dentists. JMIR Public Health Surveill 2020; 6: e18798.
4. Rubin JG, Slovin M, Krochak M. Th e Psychodynamics of Dental Anxiety and Dental Phobia. Dental Clin North Am 1988; 32: 647-56.
5. Spielbergerr CD, Goursuch RL, Lushene RE. Manuel for the State-Trait Anxiety Invertory. California: Consulting Psychologists Press.1970.
6. Öner N, Le Compte A. Durumluk ve Sürekli Kaygı Envanteri El Kitabı. 2. Baskı. İstanbul Boğaziçi Üniversitesi Yayınları. 1998.
7. Joos, A. Psychosomatic medicine and COVID-19 pandemic. Psychotherapy and Psychosomatics 2020; 89: 263-64.
8. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE 2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020; 14: 185-92.
9. Coulthard P. Dentistry and coronavirus (COVID-19) - moral decision-making. Br Dent J 2020; 228: 503–5.
10. Lau JTF, Yang X, Pang E, Tsui HY, Wong E, Wing YK. SARS-related perceptions in Hong Kong. Emerg Infect Dis 2005; 11: 417-24.
11. Çırakoğlu OC. Domuz gribi (H1N1) salgını ile ilgili algıların, kaygı ve kaçınma düzeyi değişkenleri bağlamında incelenmesi. Türk Psikoloji Bülteni 2011; 26: 48-64.
12. Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the ınitial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in china. Environment Res Public Health 2020; 17: 1729.
13. Göksu Ö, Kumcağız H. COVID-19 salgınında bireylerde algılanan stres düzeyi ve kaygı düzeyleri. Turk Stud 2020; 15: 463-79.
14. Zhang W, Wang K, Yin L, et al. Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in china. Psychother Psychosom 2020; 89: 242–50.
15. Erdur B, Ergin A, Turkcuer I, Parlak I, Ergin N, Boz B. A study of depression and anxiety among doctors working in emergency units in Denizli, Turkey. Emerg Med J 2006; 23: 759-63.
16. Kutanis RU, Tunç T. Hemşirelerde benlik saygısı ile durumluk ve sürekli kaygı arasındaki ilişki: Bir üniversite hastanesi örneği. "İş, güç". Endüstri İlişkileri ve İnsan Kaynakları Derg 2013; 15: 1-15.
17. Shevlin M, McBride O, Murphy J, et al . Anxiety, depression, traumatic stress, and COVID-19 related anxiety in the ukgeneral population during the COVID-19 pandemic. UK population mental health and COVID-19. BJPsych Open 2020; 6: 1-25.
18. Bohlken J, Schömig F, Lemke MR, Pumberger M, Heller SG. COVID-19 pandemic: Stress experience of healthcare workers-A short current review Psychiatr Prax 2020; 47: 190-7.
19. Joos A. Psychosomatic medicine and COVID-19 pandemic. Psychother Psychosom 2020; 89: 263–4.
20. Sahin O, Sahin SC. Türkiye'de COVID-19 normalleşme sürecinde hastaların dental tedavilere bakış açısının ve kurum tercihlerinin incelenmesi. Ankara Med J 2020; 4: 869-81.
21. Ovalıoğlu Z, Bozkurt DA, Akman M. COVID-19 pandemi sürecinde endodonti kliniğine gelen hasta anksiyete düzeyi. NEU Dent J 2020; 2: 98-102.
22. Moffat RC, Yentes CT, Crookston BT, West JH. Patient Perceptions about Professional Dental Services during the COVID-19 Pandemic. JDR Clin Trans Res 2021; 6: 15-23.

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The evaluation of postural characteristics in rehabilitation professionals and its effect on pain, quality of life, and sleep level

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ABSTRACT

Aim: Rehabilitation professionals play a primary role in patients' medical procedures, leaving them in long-term, fixed, and sometimes less than optimal body positions, leading to musculoskeletal disorders in individuals. This study aims to assess the postural characteristics of the rehabilitation professionals, investigate the effects on pain, quality of life, sleep levels, and identify possible risk factors.

Material and Method: Our study had 105 participants and was performed as a prospective, cross-sectional study. The demographic information of the individuals included in the study, whether they have any pain complaints related to the musculoskeletal system; if any, its localization and sleep level were evaluated. Participants were administered the Visual Analogue Scale (VAS) and the Employee Quality of Life Scale. The postural status was assessed using the Corbin Posture Scale.

Results: It was detected that the participants with higher Corbin Posture Scale scores had more severe pain levels assessed by VAS score (p:0.000, r:0.803), longer duration of musculoskeletal pain (p:0.000, r:0.456), and shorter daily sleep duration time (p:0.000,r:-0.424) as a result of our study.

Conclusion: Postural dysfunction in rehabilitation professionals leads to many medical problems, especially musculoskeletal pain, high analgesic consumption, and sleep disturbances. As a result, there may be a reduction in quality of life. Preventive postural exercise programs can also be beneficial.

Keywords: Rehabilitation, healthcare professionals, posture

INTRODUCTION

The concept of posture is defined as the positioning of each body part in the most appropriate position to the adjacent segment and the whole body. Depending on immobility and occupational demands, long-term fixation of the body in a particular position during work can cause severe postural problems (1). One of these problems is undoubtedly musculoskeletal pain. Individuals may have painful spasms and regional muscle weakness as a result of poor posture. Since the rehabilitation professionals play a primary role in various medical procedures, such as conducting physical examinations of patients, caregiving, providing hygiene, positioning, monitoring vital functions, taking blood samples, applying medications, implement of physical therapy modalities, planning and manufacturing orthotic materials, preparation medical documents and reports; they remain in fixed and sometimes non-optimal positions of the body, which can lead to diseases of the musculoskeletal system for a long time. There are few studies in literature which determines the musculokeletal complaints in rehabilitation professionals (2,3,4). In a study by Islam et al. (2) it was revealed that ninety-five percent of the participants complained of work related pain and most of the participants reported pain in the lower back (n=84) followed by upper back (n=71) and neck (n=66) . In another study by Alnaser et al. (3) it was detected that the lower back and muscle spasm were the most common body injured area among the physical therapists and manual therapy techniques and patient transfers were most common activities associated with injuries. It was concluded in a study by Devreux et al. (4) that the musculoskeletal disorders expressed by rehabilitation staff in the area of Jeddah appeared to be strongly related to the level of over-commitment in work and the main symptoms were back pain and generalized myalgia which were severe

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enough to lead to sick leave and medical consultations. According to our knowledge, this is the first study which determines the postural characteristics in rehabilitation professionals. This study also aims to evaluate the effects of postural characteristics on pain, quality of life, and sleep levels in rehabilitation professionals. The study results will be used to guide protective measures for health personnel working in the area concerned.

MATERIAL AND METHOD

Our study was performed as a prospective and cross-sectional study in a tertiary rehabilitation center. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was approved by Ankara City Hospital No. 1 Clinical Researchs Ethics Committee (Date: 19.08.2020, Decision No: E1/1030/2020) and all participants signed the informed consent form. Inclusion criteria for the study were being aged between 18 and 65 years and working as a rehabilitation professional regardless of gender. Exclusion criteria were defined as having major general health problems or refusing to participate the study.

The demographic information (age, gender, height, weight, body mass index, etc.) of the participants enrolled in the study was recorded. Additionally; the number of patients treated per day, the number of years worked, weekly hours of work, and daily hours of work was calculated. It was examined whether the participants had any complaints of musculoskeletal pain; if any, in which body part they described the most severe pain and how long the pain had been present. The Visual Analogue Scale (VAS) score was used to assess the subjects' pain intensity level. This scale consists of a 10 points line drawn on a horizontal or vertical axis with scores ranging from "0 points" for "no pain" to "10 point" for "worst pain". Participants were asked to score or mark the level that corresponded to the severity of their pain (5). We also evaluated participant's status of consulting a doctor, medical diagnosis, the types of treatments they received, and analgesic consumption per week. Participants' sleep disturbances and daily sleep duration (hours) were also examined.

The Professional Qualitiy of Life Scale is an instrument consisting of 30 items in aim to evaluate participants' positive and negative experiences that may arise from their job characteristics. The participants were asked to assign a score between 0 and 5 for each item on the scale. Although the total score is obtained as a result of these responses; the score of the "job satisfaction subscale" is obtained as a result of the responses to the first ten questions, the score of the "burnout subscale" is the result of the responses to the second 10-question section. As a result of the responses to the third 10-question section, the score of the "compassion fatigue subscale" was calculated (6).

The Corbin Posture Scale is a postural assessment scale that evaluates the inclination of the head in different directions, the shape of the dorsal region, the presence of scapula and shoulder protraction, the signs of scoliosis, kyphosis, lordosis, whether there is a difference in the height of the two shoulders and hips, the sagging status in the abdominal region, the presence of gibbosity, genu recurvatum, and the level of anterior balance by assigning a score between 0-3 (7).

Statistical analyses were performed using SPSS version 16 software. The parameters of mean, standard deviation, minimum, and maximum values were defined. The Kolmogorov-Smirnov test was used to determine whether the obtained parameters conformed to a normal distribution. Independent samples t test was used to compare the parameters between gender groups.While investigating the associations between non-normally distributed or ordinal variables, the correlation coefficients (r) and their significance (p) were calculated using the Spearman test. A probability value of $p<0.05$ was considered statistically significant.

RESULTS

The study included 105 healthcare professionals working in the field of rehabilitation. 66.66% of participants were female (n= 70), 33.33% were male (n= 35). 9.5% of the participants included in our study were physicians (n=10), 31.4% were nurses (n=33), 15.2% were physiotherapists (n=16), 12.4% were orthotic and prosthetic technician (n=13), 9.5% were secretaries (n=10) and 21.9% were clinical support staff (n=23). The mean age of the participants was 38.82±0.88. The average working time of the healthcare professionals was 15.94±0.87 years, the average weekly working duration was 41.30±0.42 hours, and the daily working time was 8.17±0.11 hours. The mean number of patients caring during the day was found to be 10.62±0.57 (**Table 1**).

Table 1. The Socio-demographic characteristics of the participants

	Mean±Standart deviation
Age	38.82±0.88
Body mass index (kg/m²)	25.33±0.36
Years of experience	15.94±0.87
Weekly working time (hours)	41.30±0.42
Daily working time(hours)	8.17±0.11
Number of patients cared for per day	10.62±0.57
Gender	**n (%)**
Female	70 (66.66%)
Male	35 (33.33%)
Job Groups	**n (%)**
Physician	10 (9.5%)
Nurse	33 (31.4%)
Physiotherapist	16 (15.2%)
Orthotic-prosthetic technician	13 (9.5%)
Medical secretary	10 (21.9%)
Total number of participants n=105	

While 86.7% (n=91) of participants described pain related to the musculoskeletal system, 13.3% (n=14) reported no pain in any part of their body. 13.3% (n=14) of the subjects have described the cervical region, 1% (n=1) the thoracic region, 10.5% (n=11) the dorsal region, 31.4% (n=33) the lumbar region, 1% i (n=1) the sacral region, 13.3% (n=14) the shoulder region, 1.9% (n=2) the elbow region, 3.8% (n=4) the hand/wrist region, % 1 (n=1) the hip region, 8.6% (n=9) the knee region and 1% (n=1) the foot/ankle region as the of most severe pain location. The participants' mean pain duration was found as 43.20±4.60 months. 46.7% (n=49) of participants consulted a doctor due to their musculoskeletal pain, 23.8% (n=25) of the participants stated that they wanted to consult a doctor but could not yet, 29.5% (n=31) reported that they did not need medical support. The diagnosis of the rehabilitation professionals who had consulted a doctor were osteoarthritis (17.1%) (n=18), rheumatoid arthritis (1%)(n=1), disc herniation (14.3%) (n=15), meniscal degeneration (2.9%) (n=3), tendinitis (7.6%)(n=8), sacroiliitis (1%) (n=1), scoliosis (1.9%) (n=2), myofascial pain syndrome (1%) (n=1) (**Table 2**). 46.7% of healthcare professionals reported that they did not receive any treatment for their musculoskeletal complaints, 21% (n=22) of participants reported that they used analgesics, 20% (n=21) received exercise therapy, and 12.4% (n=13) reported that they received a physiotherapy program. The mean VAS score of the participants was found to be 5.81±0.32. It was found that the mean number of analgesic consumption by the participants was 7.36±0.68 per week. It was found that 54.3% (n=57) of the health professionals who participated in our study had sleep problems. The average sleep duration of the participants was found to be 6.60 ±0.13 hours per day. The mean Corbin Posture Scale score used to examine the postural dysfunction of the individuals included in our study was found to be 5.59±0.26. The total mean score of the Professional Quality of Life Scale, which was used to assess the participants' quality of life was 76.31±1.41. The average score of the "Job satisfaction" subscale was 23.83±0.54, the mean score of the "burnout" subscale was 27.89±0.55, and the mean score of "compassion fatigue" subscale was 24.58±0.54 (**Table 3**). The comparision of patient characteristics according to gender revealed that there was a statistically significant difference in age (p:0.039) and body mass indeks (p<0.001) parameters between female and male groups; no statistically significant difference was detected in other parameters (**Table 4**).

Table 2. The pain characteristics of the participants

Presence of musculoskeletal pain	**n (%)**
Yes	91 (86.7%)
No	14 (13.3%)
Pain localization	**n (%)**
Cervical region	14 (13.3%)
Thoracic region	1 (1%)
Dorsal region	11 (10.5%)
Lumbar region	33 (31.4%)
Sacral region	1 (1%)
Shoulder region	14 (13.3%)
Elbow region	2 (1.9%)
Hand/Wrist region	4 (3.8%)
Hip region	1 (1%)
Knee region	9 (8.6%)
Foot/Ankle region	1 (1%)
Diagnoses of participants	**n (%)**
Osteoarthritis	18 (17.1%)
Rheumatoid arthritis	1 (1%)
Disc herniation	15 (14.3%)
Meniscus degeneration	3 (2.9%)
Tendinitis	8 (7.6%)
Sacroiliitis	1 (1%)
Scoliosis	2 (1.9%)
Myofascial pain syndrome	1 (1%)

Table 3. The results of participants' scale scores

	Mean±Standart Deviation
VAS value	5.81±0.32
Corbin Posture Scale Score	5.59±0.26
The Professional Qualitiy of Life Scale -Job Satisfaction subscale score	23.83±0.54
The Professional Qualitiy of Life Scale -Burnout subscale score	27.89±0.55
The Professional Qualitiy of Life Scale -Compassion fatigue subscale score	24.58±0.54
The Professional Qualitiy of Life Scale -Total score	76.31±1.41

Table 4. The comparision of patient characteristics between genders

	Female (n=67) Mean±SD	**Male (n=38) Mean±SD**	**p**
Age	37.68±8.32	41.44±9.77	0.039
Body mass index (kg/m²)	24.33±3.78	27.12±2.95	0.000
Years of experience	15.18±8.95	16.94±9.01	0.337
Weekly working time (hours)	40.98±4.45	41.86±4.14	0.319
Daily working time (hours)	8.25±1.44	8.02±0.16	0.208
Number of patients cared for per day	11.46±6.01	11.05±5.56	0.731
Pain duration (month)	47.80±49.82	35.10±41.65	0.187
Analgesic consumption per week	7.40±6.84	7.28±6.73	0.935
VAS value	6.14±3.03	5.23±3.73	0.204
Corbin Posture Scale Score	5.89±2.67	5.05±2.75	0.128
The Professional Qualitiy of Life Scale -Total score	76.83±12.96	75.39±17.01	0.627
Sleep duration (hour/day)	6.46±1.37	6.84±1.26	0.165

It was also detected that rehabilitation professionals with longer years of work had longer musculoskeletal pain duration (p:0.002, r:0.30), had higher VAS scores (p:0.006, r:0.267), and greater consumption of analgesics per week (p:0.001, r:0.309). As the number of patients that the rehabilitation professionals deal with during the day had increased, it was found that their pain duration (p:0.000, r: 0.498), VAS score (p:0.000, r:0.801), and the number of analgesic consumption per week had an increment (p:0.000, r:0.720). When the effect of rehabilitation professionals' postural status on other parameters were examined; it was revealed that the health professionals with higher Corbin Posture Scale scores were dealing with more patients (p:0.000, r:0.636) (**Figure 1**) had higher VAS scores (p:0.000, r:0.803) (**Figure 2**), longer pain durations (month) (p:0.000, r:0.456) (**Figure 3**), greater consumption of analgesics per week (p:0.000, r:0.608). Furthermore; a positive correlation was found between the Corbin Posture Scale score and the total score of the the Professional Quality of Life Scale scres (p:0.022, r:0.223). No statistically significant correleation was found in the occupational satisfaction subscale scores and the burnout subscale scores of the Professional Quality of Life Scale with other parameters. (p>0.05). However; a positive correlation was detected between this scale's compassion fatigue subscale score and the age of the healthcare professionals (p:0.047, r:0.195). It was also found that there was a significant reduction in sleep duration of participants who had deal with higher number of patients per day (p:0.000, r:-0.494); had longer duration of musculoskeletal pain, (p:0.000, r:-0.383), had higher VAS scores (p:0.000, r:-0.543) and had higher Corbin Posture Scale scores (p:0.000,r:-0.424) (**Figure 4**).

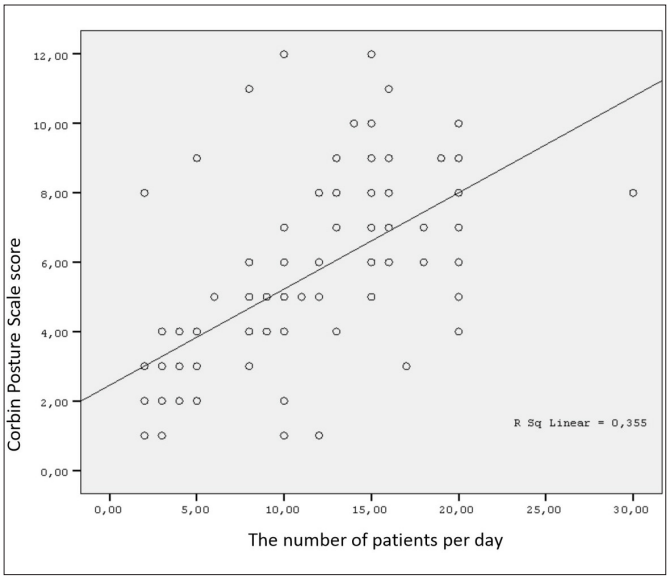

Figure 1. The correlation between Corbin Posture Scale scores and the number of patients cared for during the day

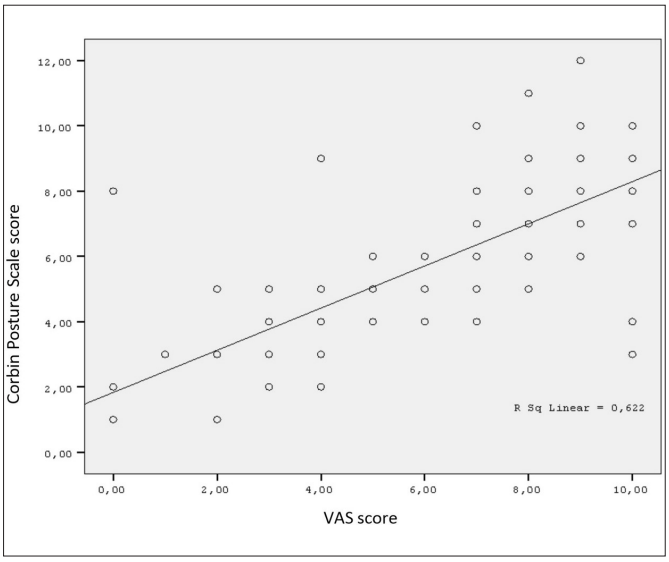

Figure 2. The correlation between Corbin Posture Scale scores and VAS scores

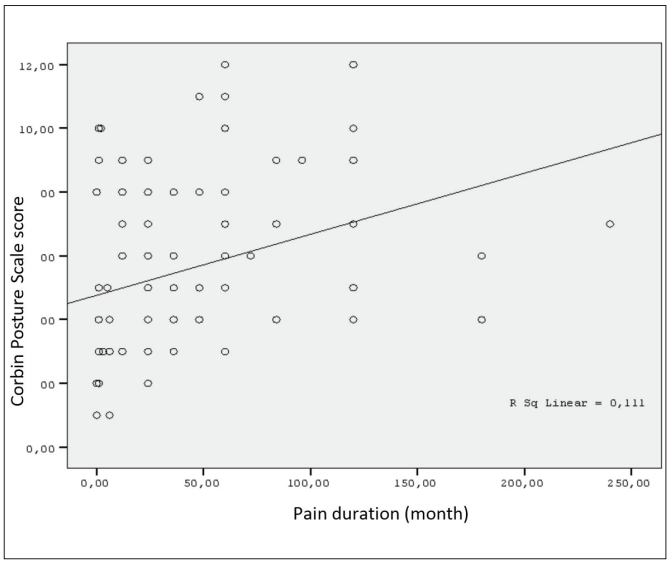

Figure 3. The correlation between Corbin Posture Scale scores and pain durations (months)

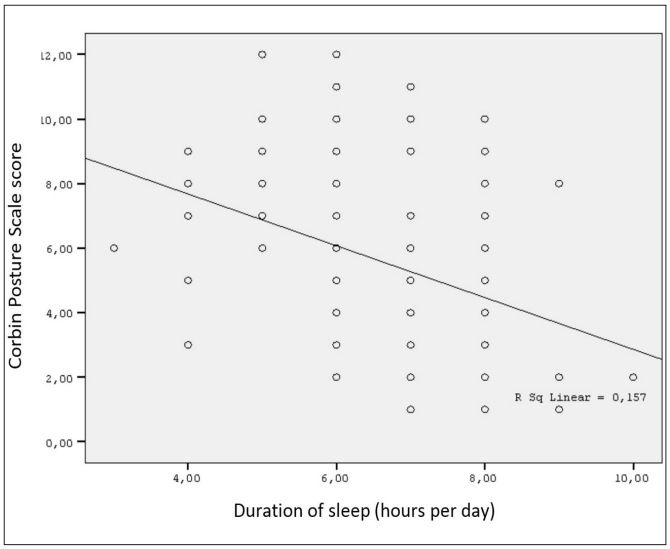

Figure 4. The correlation between Corbin Posture Scale scores and daily sleep durations (hours)

DISCUSSION

The relationship between the postural status of rehabilitation professionals and the level of musculoskeletal pain was revealed in our study. The rehabilitation professionals with postural impairments were found to have more severe pain complaints, longer pain duration, and more analgesic consumption per week. It has been observed that this situation leads to a deterioration in the quality of life. In a study by Küçük et al. (8) that included 213 office workers, it was found that 48.4% of the participants worked in a static seated posture with the neck bent forward in the work environment. In addition, it was found that these individuals experienced spinal pain 6.57±7.11 times per week, and concluded that the defined postural dysfunction may cause spinal pain more frequently in the participants.

In another study by Ribeiro et al. (9) which examines the musculoskeletal system problems of nurses according to their work lifes; it has been reported that the frequency of musculoskeletal system complaints had increased in participants who had longer years of work experience. Additionally; standing (48.8%), forward bending of the trunk (42.3%), trunk rotation (40.6%), excessive use of force on hands and fingers (37.3%), sitting (36.6%), and repetitive arm movements (34.3%) were defined as risky movements observed in participants during the work which may lead to musculoskeletal problems in the same study (9). The results of our study revealed that rehabilitation professionals who have been working for longer years had longer pain durations, higher VAS scores and more analgesic consumption per week.

Ezzatvar et al. (10) showed in their study, which evaluated the impact of physiotherapist workload on musculoskeletal pain, that participants who deal with more than 30 patients per week had higher levels of musculoskeletal pain. Similarly, we have found in our study that the rehabilitation professionals who deal with more patients during the day had longer pain durations, higher VAS scores, higher amount of analgesic consumption per week, and higher levels of postural dysfunctions. During the rehabilitation procedures such as performing physical examination of the patients, the administration of their medical treatments, the collection of blood and urine samples, the positioning, providing patient transfer, the application of physiotherapy techniques, the production of orthotics and prosthesis materials, the registration of medical documents; the rehabilitation professionals may have positioned in postures that are not appropriate for body biomechanics. As the number of patients dealt with during the day increases, the time spent in inappropriate postures of healthcare professionals also has an increment. As a result; it plays a role in the development of various posture disorders as dropped shoulder, increment in thoracic kyphosis, reduction in both cervical lordosis and lumbar lordosis.

In a study by Tolu et al. (11) (2019), which examined the musculoskeletal problems of anesthesiologists, it was reported that the musculoskeletal complaints of the participants were observed in the regions of low back (51.2%), neck (42.3%), knee (35.8%), shoulder (29.3%), foot/ankle (28.5%), back (26%), elbow (22%), hip/thigh (19.5%) and hand/wrist (14.6%) . In accordance with these findings, the rehabilitation professionals have described low back, neck, shoulder and back regions as the most painful localizations of their body in our study. Rehabilitation professionals usually keep their bodies in inappropriate, static, flexion postures for a long time to perform patients' rehabilitation procedures; as a result the formation of pathological muscle spasms and extra load transferring to joints may occur and this process also leads to musculoskeletal pain (11,12).

In a study by Harrison et al. (13) the relationship between sleep level and musculoskeletal system problems has been revealed and it has been concluded that the severity of pain has a statistically significant positive correleation with sleep disorders. Similarly, it was detected that rehabilitation professionals with lower daily sleep durations have longer duration of musculoskeletal pain, and higher VAS scores in our study.

CONCLUSION

The results of our study revealed the effect of rehabilitation professionals' postural status on pain, sleep level, and quality of life. Postural disorders in individuals lead to many medical problems, including musculoskeletal pain, high analgesic consumption, and sleep disturbances. As a result, there may be a reduction in the quality of life. Therefore, it is of great importance to detect postural disorders of rehabilitation professionals as early as possible, follow up their musculoskeletal complaints for a long time, treat existing pathologies, and provide protective exercise programs in necessary conditions..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Ankara City Hospital No. 1 Clinical Researchs Ethics Committee (Date: 19.08.2020, Decision No: E1/1030/2020)

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. Tufan AD, Karabuğa B, Simay B, et al. Postür ve postür bozuklukları. Fizyoterapi Reh Derg 1996; 8: 1-10.
2. Islam MS, Habib MM, Hafez MA,et al. Musculoskeletal complaints among physiotherapy and occupational therapy rehabilitation professionals in Bangladesh. Work 2015; 50: 379-86.
3. Alnaser MZ, Aljadi SH. Physical therapists with work-related musculoskeletal disorders in the State of Kuwait: A comparison across countries and health care professions. Work 2019; 63: 261-68.
4. Devreux ICN, Al-Awa B, Mamdouh K, et al. Relation of work-related musculoskeletal disorders and over-commitment of rehabilitation staff in Saudi Arabia. Life Sci J 2012; 9: 781-85
5. Keele KD. The pain chart. Lancet 1948; 2: 6-8.
6. Yeşil A, Ergün Ü, Amasyalı C, et al. Çalışanlar için yaşam kalitesi ölçeği Türkçe uyarlaması geçerlik ve güvenilirlik çalışması. Nöropsikiyatri Arşivi 2010; 47: 111-7.
7. Corbin C, Welk G, Corbin W, Welk K. Concepts of fitness and wellness: A comprehensive lifestyle approach. In: McGraw-Hill Companies, Incorporated; 2008.
8. Küçük F, Düzenli ÖS, Şenol H , Özkeskin M . Ofis çalışanlarında çalışma postürü, kas iskelet sistemi rahatsızlıkları, bel ağrısına bağlı özürlülük düzeyi ve sağlıkla ilgili yaşam kalitesinin incelenmesi. Ergoterapi ve Rehabilitasyon Derg 2018; 6: 135-44.
9. Ribeiro T, Serranheira F, Loureiro H. Work related musculoskeletal disorders in primary health care nurses. Appl Nurs Res 2017; 33: 72-7
10. Ezzatvar Y, Calatayud J, Andersen LL, Aiguadé R, Benítez J, Casaña J. Professional experience, work setting, work posture and workload influence the risk for musculoskeletal pain among physical therapists: a cross-sectional study. Int Arch Occupat Environment Health 2020; 93: 189-96.
11. Tolu S BB. Work-related musculoskeletal disorders in anesthesiologists: A cross-sectional study on prevalence and risk factors. Ann Med Res 2019; 26 :1406-14.
12. Szeto GP, Cheng SW, Poon JT, Ting AC, Tsang RC, Ho P. Surgeons' static posture and movement repetitions in open and laparoscopic surgery. J Surg Res 2012; 172: 9-31.
13. Harrison L, Wilson S, Munafò MR. Exploring the associations between sleep problems and chronic musculoskeletal pain in adolescents: a prospective cohort study. Pain Res Manag 2014; 19: 139-45.

Original Article

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The impact of COVID-19 on rural population: A retrospective study

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ABSTRACT

Objective: The COVID-19 outbreak became a major global health concern. There are some differences between urban and rural areas that may determine the impact of a viral pandemic. In our study, we aimed to investigate and present epidemiological, demographic, clinical, and radiological data relating to a rural area.

Material and Method: This retrospective two-center study involved 2234 patients tested for COVID-19 between March 30th and July 15th, 2020. All patients were analysed for clinical, demographic, and radiological data.

Results: Of the patients; 1309 (58.6%) were male, 925 (41.4%) female and 259 (11%) were PCR positive, and 1975 (89%) PCR negative. Of the PCR positive group, 121 (46.7%) were male and 138 (53.3%) female. The mean age was 38 ±18.5. Twenty-nine (11.2%) patients needed intensive care support. Twelve (4.6%) patients died due to COVID-19: two of them due to COVID-19-related myocardial infarction and ten of them due to severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan dysfunction, or septic shock. The case fatality rate (CFR) was 4.6%.

Conclusion: Age, sex, hypertension, diabetes, asthma, and heart failure were associated with COVID-19 infection. The risk of infection was higher in patients older than 20 years ($p<0.001$) and females (OR: 1.636; $p<0.001$). Patients with hypertension (OR: 2.281; $p<0.001$), diabetes (OR: 1.013; $p=0.039$), asthma (OR: 2.786; $p=0.001$) or heart failure (OR: 2.610; $p=0.006$) had a significantly higher risk of infection.

Keywords: COVID-19, Viral pandemic, Rural area

INTRODUCTION

In December 2019, a cluster of unidentified pneumonia cases appeared in Wuhan, China. The National Health Commission (NHC) of the People's Republic of China later announced that a novel coronavirus was responsible for the outbreak (1). The virus is genetically similar to bat coronaviruses and shares about 79% and 50% of its genetic sequence with the coronaviruses that are responsible for the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), respectively (2). The virus, named the 2019 novel coronavirus (2019-nCoV), has rapidly spread across China and other countries and has become a major global health concern. On February 11th 2020, the World Health Organization (WHO) announced a name for the epidemic disease caused by 2019-nCoV: coronavirus disease (COVID-19) (3). Evidence of human-to-human transmission through respiratory droplets, contact and, even fecal-oral transmission was found (4). Because of its high transmissibility and its incubation period, the number of cases worldwide has reached approximately 11 million, with 404,396 deaths (5).

While some infected patients present with symptoms of mild respiratory tract infection, some develop severe pneumonia, ARDS, or multiple organ failure, leading to death (5).

According to a recent analysis, male patients have a markedly increased risk of developing a severe disease compared with females (6). Smoking and the presence of concomitant diseases such as hypertension, diabetes, cardiovascular disease, and respiratory disease are factors significantly associated with a severe prognosis (7).

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Although clinical features of COVID-19 include a dry cough, fever, diarrhea, vomiting, and myalgia, some patients with multiple comorbidities present with severe infection complications such as acute kidney injury (AKI) and symptoms of ARDS. Currently, there are few studies that define the pathophysiological characteristics of COVID-19, and there is an uncertainty about its mechanism of spread. Basic hand hygiene, avoiding travel to high-risk areas, and avoiding contact with symptomatic individuals are all important in preventing the disease despite on going vaccine development for COVID-19 (8,9).

Since rural regions have distinct demographic and health infrastructure issues requiring tailored approaches to service delivery, there are few studies about the effects of the COVID-19 pandemic on rural populations. Adıyaman is a province in south-central Turkey that has an area of 7,606.16 km^2 and a population of 626,465 as of 2019 (**Figure 1**). In our study, we aimed to present clinical and demographic data relating to patients from two neighboring rural areas in Turkey.

Figure 1. Turkey map showing the location of Adıyaman province

MATERIAL AND METHOD

Study Design and Clinical Parameters

The study included 2234 patients from two centers in Adiyaman, Turkey between March 30th and July 15th, 2020. Clinical, medical history, and radiological data were obtained through the electronic patient database retrospectively. Patients who had signs and symptoms of acute respiratory disease or clinical symptoms that could not be explained by any other cause/disease, individuals with or without symptoms who had spent more than 15 minutes with or had been less than one meter apart from COVID-19-positive patients, individuals sharing the same home or office with infection-suspected patients , those who recently traveled abroad, and babies born from suspected COVID-19-positive mothers were included. Individuals who had not been in contact with COVID-19-positive patients, had no recent history of travel abroad, and had no complaints were excluded. A combination of nasopharyngeal and oropharyngeal swabs were taken. Reverse transcription-polymerase chain reaction (RT-PCR) results were considered the reference standard. The swab test was repeated at least one day later in patients who had typical symptoms and positive CT findings but negative test results. The formula below was used to measure the case fatality rate (CFR):

CFR (%)=(Number of deaths due to COVID-19/ Number of closed cases of COVID-19)×100.

Ethics This study was approved by Clinical Research Ethics Committee of Adıyaman University (Date 21.07.2020, Decision No: 2020/7-32). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Imaging Interpretation

Chest X-ray (CXR) was the first-line imaging modality used for patients with suspected COVID-19. Computed tomography (CT) was performed in patients with positive X-ray findings, such as the presence of bilateral nodular/ peripheral ground-glass opacities and consolidation. The CT and CXR images of the relevant patients were reviewed by two thoracic radiologists who were not privy the patients' test results. Ground-glass opacities (GGO), a crazy-paving pattern appearance, vascular dilatation in the area of GGO, air space consolidation, bronchovascular thickening in the lesion, and traction bronchiectasis were reported as positive CT findings. The CO-RADS classification system was used to assess the pulmonary involvement of COVID-19. According to this scoring system, numbers ranging from one to five (1. < 5% involvement; 2. 5%–25% involvement; 3. 26%–49% involvement; 4. 50%–75% involvement; 5. > 75% involvement) are used and reflect the severity of the disease.

Statistical Analysis

Statistical analyses were applied using SPSS 23 for Windows (SPSS Inc., Chicago, IL, U.SA.). The distribution of the variables was examined using the Kolmogorov–Smirnov test. The continuous variables, depending on whether they had normal distribution or not, were presented as mean ± standard deviation or median ± interquartile range, respectively. The categorical variables were displayed as percentages.

For the comparison between the PCR positive group and the PCR negative group, the Mann–Whitney U test and the Chi-squared test were appropriately used. Additionally, after the Chi-squared test for age groups was applied, post-hoc testing with the Bonferroni adjustment was carried out to determine the age group that was significant (10).

Binomial logistic regression analysis was also performed to evaluate the impact of variables found significant in **Table 4** on the odds ratio for the eventuality of COVID-

19-positive cases. In all analyses (except the age group variables in **Table 1**, where because of the Bonferroni adjustment, the p-value was accepted as 0.006 for these variables), two-tailed $p < 0.05$ was accepted as statistically significant.

Table 1. Patient demographics and baseline characteristics

	PCR (+) (n=259)	PCR (-) (n=1975)	p value
Age (years)	38 ±18.5	33 ±11	0.030*
Age <6 (n, %)	11 (4.2 %)	57 (2.9 %)	0.230
Age 6-20 (n, %)	48 (18.5 %)	270 (13.7 %)	0.035
Age 21-50 (n, %)	117 (45.2 %)	1248 (63.2 %)	<0.001*
Age >50 (n, %)	83 (32 %)	400 (20.3 %)	<0.001*
Sex (n, %)			<0.001*
Male	121 (46.7 %)	1188 (60.1%)	<0.001*
Female	138 (53.3 %)	787 (39.9 %)	<0.001*
Hypertension (n, %)	56 (21.6 %)	197 (10 %)	<0.001*
DM (n, %)	27 (10.4 %)	77 (3.9 %)	<0.001*
Smoking (n, %)	74 (28.6 %)	624 (31.6 %)	0.354
COPD (n, %)	15 (5.8 %)	66 (3.3 %)	0.162
Asthma (n, %)	16 (6.2 %)	39 (2 %)	0.001*
Heart Failure (n, %)	19 (7.3 %)	35 (1.8 %)	<0.001*
Symptomatic (n, %)	148 (57.1 %)	414 (21 %)	<0.001*
Fever	66 (44.3 %)	97 (4.9 %)	<0.001*
Cough	140 (93.3 %)	364 (18.4 %)	0.087
Shortness of breath	62 (41.6 %)	198 (10 %)	0.213
Tiredness	78 (52.3 %)	103 (5.2 %)	<0.001*
Headache	23 (15.4 %)	34 (1.7 %)	0.017*
Myalgia	34 (22.8 %)	59 (3 %)	0.021*
Diarrhea (n, %)	6 (4 %)	1 (0.1 %)	0.002*

Abbrveviations: * means statistically significant. COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus

RESULTS

This retrospective study involved 2234 patients being tested for COVID-19. The patients' symptoms, risk factors, and other demographic data are presented in **Table 1**. Of the patients, 1307 (58.5%) were male and 925 (41.4%) were female. There were 259 (11%) PCR positive and 1975 (89%) PCR negative patients.

In the PCR negative group, 1188 (60.1%) patients were male and 787 (39.9%) were female. The mean age was 33 ±11. The number of medical staff was 282 (14 %). Thirty-nine (1.9%) patients had a history of contact with people from a foreign country, including contact made when traveling abroad. In terms of clinical risk factors, 197 (10%) patients had hypertension, 77 (3.9%) DM, 66 (3.3%) COPD, 39 (2%) asthma, 35 (1.8%) HF, and 414 (21%) were smokers (**Figure 2**). On admission, 414 (21%) patients were symptomatic and 1561 (79%) were asymptomatic. The most common symptoms were a cough and shortness of breath.

In the PCR positive group, 121 (46.7%) patients were male and 138 (53.3%) were female. The mean age was 38 ±18.5. Six (2.3%) patients were medical staff. Seven (2.7%) patients had a history of contact with people from foreign countries, including contact made when traveling abroad. In terms of clinical risk factors, 56 (21.6%) patients had hypertension, 27 (10.4%) DM, 15 (5.8%) COPD, 16 (6.2%) asthma, 19 (7.3%) HF, and 74 (28.6%) were smokers (**Figure 2**). On admission, 148 (57.1%) of patients were symptomatic and 111 (42.9%) were asymptomatic. Most of the symptoms reported were a cough, fever, shortness of breath, and tiredness. Other symptoms included a headache, myalgia, and diarrhea.

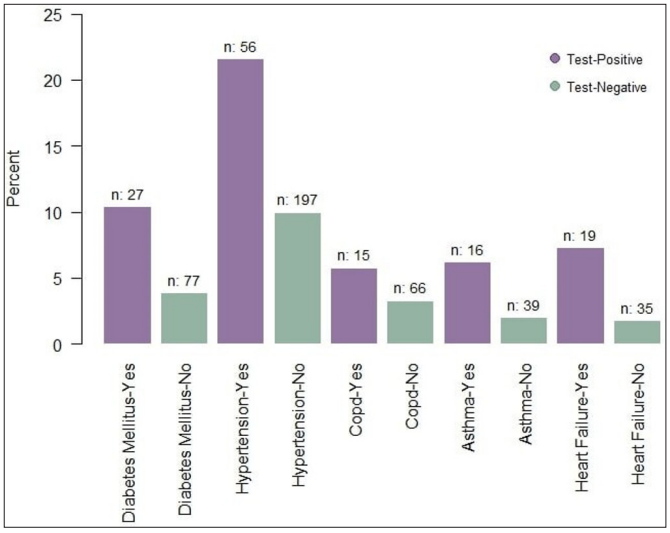

Figure 2. Graphic showing the proportion of comorbid diseases of patients

Table 2 provides information about test numbers, CT findings, treatment, and prognoses. The mean test number was 1.21±0.5. 465 CT scans were performed, 131 of them were PCR positive. According to the CT results, typical findings such as GGO, a crazy-paving pattern appearance, vascular dilatation in the area of GGO, air space consolidation, bronchovascular thickening in the lesion, and traction bronchiectasis were detected in 160 (7.2%) patients. Eighty-nine of them were PCR positive. The data on CT scores for the PCR positive patients are presented in **Table 3**.

In accordance with their test results and clinical status, 2017 (90.3%) patients were discharged and recommended treatment and/or isolation at home, 152 (6.7%) patients needed medical treatment in hospital and 65 (3%) patients needed intensive care support, including non-invasive mechanical ventilation. Of the PCR positive patients, 156 (60.2%) were recommended isolation and treatment at home, 74 (28.6%) were hospitalized in service during treatment, and 29 (11.2%) needed intensive care support. Medical treatment was applied in (selected) patients according to guidelines. The antibiotics were used in

cases of generally covered common pathogens and some atypical pathogens. When secondary bacterial infection occurred, medication was administered according to the bacterial culture and drug sensitivity results. Steroids were used in selected cases as well.

Table 2. Test numbers, infection rates and prognosis of patients

	All (n=2234)	PCR (+) (n=259)
Test (number, means)	1.21±0.5	2 .14±0.51
CT (n, %)	465 (20.8%)	131 (51%)
Infection (n, %)	184 (8.2%)	89 (34%)
COVID-19 typical findings	160 (7.2%)	89 (34%)
Other (bacterial, fungal..)	24 (1%)	0 (0%)
Contamination origin (n, %)		
Local	2188 (97.9%)	252 (97.3%)
Outside	46 (2.1%)	7 (2.7%)
Medical staff (n, %)	288 (12.9%)	6 (2.3%)
Treatment (n, %)		
Home	2017 (90.3%)	156 (60.2%)
Service	152 (6.7%)	74 (28.6%)
Intensive care	65 (3%)	29 (11.2%)
Prognosis (n, %)		
Cured	2222 (99.5%)	247 (95.4%)
Death	12 (0.5%)	12 (4.6%)

Abbreviations: CT: Computed tomography

Tablo 3. Imaging results of patients with COVID-19 pneumonia

COVID-19 positive (n=259)	CT (scores, mean)
Age group (<6)	-
Age group (6-20)	1±0
Age group (21-50)	2.71±0.19
Age group (>50)	3.72±0.19
Sex-female	3.31±0.21
Sex-male	3.03±0.19
Hypertension	4±0.19
Diabetes mellitus	3.95±0.31
Smoking	3.04±0.19
COPD	3.85±0.37
Asthma	3.91±0.39
Heart failure	3.59±0.39

Abbreviations: * means statistically significant. COPD: Chronic obstructive pulmonary disease

Of the PCR positive patients, two of them died due to COVID-19-related myocardial infarction and ten of them died due to severe pneumonia, ARDS, multiorgan dysfunction, or septic shock.

According to our study, age, sex, hypertension, diabetes, asthma, and heart failure are all associated with COVID-19 infection. It was found that females have more of an infection risk than males (OR: 1.636; p<0.001). Similarly, patients with hypertension (OR: 2.281; p<0.001), diabetes (OR: 1.013; p=0.039), asthma (OR: 2.786; p=0.001), or heart failure (OR: 2.610; p=0.006) have a higher risk of COVID-19 infection. It was also found that COVID-19 infection risk is significantly associated with age (OR: 0.991; p=0.039) (**Table 4**).

Table 4. Risk factors associated with COVID-19 infection

	β estimates with standard errors	OR	p value
Constant (β_0)	-2.154±0.172	-	<0.001*
Age (β_1)	-0.009±0.004	0.991	0.039*
Sex (β_2)	0.492±0.136	1.636	<0.001*
Hypertension (β_3)	0.825±0.237	2.281	0.001*
Diabetes (β_4)	0.558±0.006	1.013	0.039*
Asthma (β_5)	1.025±0.321	2.786	0.001*
Heart failure (β_6)	0.959±0.346	2.610	0.006*

Abbreviations: * means statistically significant.

DISCUSSION

The outbreak of COVID-19 contributed to increasing morbidity and mortality rates so was announced to be a major worldwide pandemic by the World Health Organization (11). Accordingly, recent research, in terms of understanding the mechanism of progression and transmission of COVID-19, has contributed to the development of pharmacological and non-pharmacological treatment strategies (12). The clinical manifestation of the virus in humans and the increasing number of symptomatic and asymptomatic patients each day have led to a growing concern for public health.

There are some differences between urban and rural areas that may contribute to the influence of viral transmission, diagnostics, morbidity, and mortality. Socioeconomic factors, access to healthcare, and pandemic preparedness are the main factors. In past years, the H1N1 and influenza A pandemics caused high mortality rates in rural Turkey. Now, in the U.S., there is a higher percentage of elderly in the rural population (age > 60) with co-existing diseases and, along with their smoking status, that increases the risk of infection and COVID-19-related severe complications (13, 14).

In our study, the mean age was 38 ±18.5 in the PCR positive group and 33 ±11 in the PCR negative group. We found that individuals aged 20–50 and those older than 50 years had a higher risk of COVID-19 infection (p<0.001). Although the area that we researched is rural, the population tested for COVID-19 was relatively young. The following factors were considered the reasons for this: first, the COVID-19 pandemic started in China, then spread to Asia, the United States, Turkey, and other European countries, so there was not enough time to prepare for the pandemic, and second, soon after the beginning of the pandemic, individuals over the age of 65 were prohibited from going outside and contacting other individuals. The people who were actively working and in contact with other individuals were young.

In our study, there were 259 patients in the PCR positive group. The incidence of infection in women was higher than in men (p<0.001), but the mortality rate was higher

in males than in females. Data from single-cell RNA sequencing (scRNA-seq) suggests that the number of ACE2-expressing pulmonary alveolar type II cells are higher in men than in women. The reduced susceptibility of females to viral infections may also be attributed to sex hormones that affect the regulation of immunity. Moreover, the expression of the androgen receptor (AR) is positively correlated with ACE2. This evidence is thought to account for why men have a markedly increased risk of developing severe cases compared to women (15).

Recent studies have shown that people with diabetes mellitus, hypertension, a smoking habit, COPD, asthma, or heart failure are associated with increased infection risk and a severe prognosis. A study confirmed that diabetes (22%) was one of the most evident comorbidities of 32 non-survivors from a group of 52 intensive care patients with COVID-19. COPD and asthma exacerbations are the major factors that cause worsening of symptoms, often lead to increased hospitalization and a poor prognosis. In intensive care units, infusion of fluids given to maintain blood pressure in patients with HF, as well as parenteral drug administration may cause an even higher pulmonary vascular pressure, which is already high. A pulmonary edema may accompany acute respiratory distress syndrome, which increases mortality risk (16-19). In relation to this evidence, our study confirmed that patients with hypertension (OR: 2.281; p<0.001), diabetes (OR: 1.013; p=0.039), asthma (OR:2.786; p=0.001), or heart failure (OR:2.610; p=0.006) have a higher risk of COVID-19 infection. But interestingly, in terms of infection risk, there was no difference between patients with COPD and those without (p=0.162).

Cough, fever, and shortness of breath were common symptoms in both the PCR positive and PCR negative groups. Headaches were particularly common in hypertensive patients, shortness of breath was common in patients with COPD, and diarrhea was seen only in children under six years old. Some specific symptoms, such as loss of smell and taste, were not seen in any patient.

It is cricual to screen asymptomatic carriers who are an important source of COVİD-19 infections from truly healthy populations to prevent and control spreading among individuals. A recent study showed that the presymptomatic phase and asymptomatic infections account for 47% and 6.6% of transmission (20). That is why our study included symptomatic and asymptomatic patients.

In suspected patients who are PCR negative, CT evaluation is often key in the diagnosis of infection because early recognition of disease is important for timely treatment and preventing underdiagnosing (21). In our study, 71 (3%) patients repeatedly had negative PCR test results, although they had typical symptoms and CT findings. Probably, factors such as the immature development of detection technology, low patient viral load, and improper sampling contributed to the patient's negative test results.

CT scores correlated to age and the presence of comorbid diseases. Five PCR-positive patients developed ARDS, septic shock, and followed by multiple organ failure. The CT scores of each of those patients was five. Therefore, early diagnosis and timely treatment of critical cases are crucial. COVID-19 may complicate with acute coronary syndrome and even sudden cardiac death. The patients who avoid going to hospital have a higher mortality rate due to acute coronary syndrome related complications (22). Two of COVID-19 positive patients died because of COVID-19-related sudden cardiac death. There was no evidence of drug use, co-morbid conditions, or family history of the disease. Both patients were smokers.

The case fatality rate of COVID-19 is significantly associated with age and comorbidities, across the world (23). According to a report, the overall CFR in Turkey was estimated to be 1.85%, but in our study population, the CFR was 4.6% (24). The probable reasons for the high mortality rate were socioeconomic factors, lack of adequate knowledge about COVID-19, a high percentage of smokers within the population, and co morbid disease. It should also be kept in mind that in addition to transmission within the population during the active epidemic period, infected patients who came to visit from outside areas also contributed to the increase in infections. In conclusion, considering the age stratification, pre-existing co-morbidities, relatively limited healthcare access and resources, socioeconomic status as factors, the rural population may be at risk of higher mortality. Since there is no specific antiviral drug, measures such as frequent hand washing, wearing face masks, encouraging people to social distance, and restrictions on public gatherings and non-essential travel seem to be useful in decreasing the transmission rate. Important gaps in our knowledge of the origin, epidemiology, transmission dynamics, and clinical spectrum of the disease needed to be filled by further studies.

Limitations of the Study

The first limitation is that the study population could be larger; however, the integration of multiple centers is sometimes difficult to achieve, so we included just two centers. Second, more detailed data on the clinical course of the patients and blood tests could be given. However, the data in this study provides an early assessment of the epidemiological and clinical characteristics of people tested for COVID-19 in Adiyaman, Turkey. Another

limitation of our study is that the medical treatment given to the patients included in our study was different from the current treatment guidelines (hydroxychloroquine and oseltamivir are no longer used in therapy).As we gain more information about COVID-19 and the number of cases continues to increase, further studies will be needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Clinical Researchs Ethics Committee of Adıyaman University (Date 21.07.2020, Decision No: 2020/7-32).

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

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. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. lancet 2020; 395: 497-506.
2. Chan JF-W, Yuan S, Kok K-H, 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 2020; 395: 514-23.
3. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020; 395: 470-3.
4. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med 2020.
5. 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.
6. Wei X, Xiao Y-T, Wang J, et al. Sex differences in severity and mortality among patients with COVID-19: evidence from pooled literature analysis and insights from integrated bioinformatic analysis. arXiv 200313547. 2020.
7. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect 2020; 81: e16-e25.
8. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020; 76: 71-6.
9. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol 2020; 20: 615-32.
10. Garcia-Perez MA, Nunez-Anton V. Cellwise residual analysis in two-way contingency tables. Educ Psychol Meas 2003; 63: 825-39.
11. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed Ateneo Parmense 2020; 91: 157-60.
12. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses: Springer; 2015. p. 1-23.
13. Cosby AG, McDoom-Echebiri MM, James W, Khandekar H, Brown W, Hanna HL. Growth and persistence of place-based mortality in the United States: the rural mortality penalty. Am J Public Health 2019; 109: 155-62.
14. Kirakli C, Tatar D, Cimen P, et al. Survival from severe pandemic H1N1 in urban and rural Turkey: a case series. Respir care 2011; 56: 790-5.
15. Sharma G, Volgman AS, Michos ED. Sex differences in mortality from COVID-19 pandemic: are men vulnerable and women protected?. JACC Case Rep 2020; 2: 1407-10.
16. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Resp Med 2020; 8: e21.
17. Johnston SL. Asthma and COVID-19: Is asthma a risk factor for severe outcomes?. Allergy 2020; 75: 1543-5.
18. Mehra MR, Ruschitzka F. COVID-19 Illness and Heart Failure: A Missing Link?. JACC Heart Fail 2020; 8: 512-4.
19. Alqahtani JS, Oyelade T, Aldhahir AM, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. PLoS one. 2020; 15: e0233147.
20. Moghadas SM, Fitzpatrick MC, Sah P, et al. The implications of silent transmission for the control of COVID-19 outbreaks. Proc Natl Acad Sci 2020; 117: 17513-5.
21. Bernheim A, Mei X, Huang M, et al. Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. Radiology 2020: 200463.
22. Rodriguez-Leor O, Cid-Alvarez B. ST-Segment Elevation Myocardial Infarction Care During COVID-19: Losing Sight of the Forest for the Trees. JACC Case Rep 2020; 2: 1625-7.
23. Khafaie MA, Rahim F. Cross-country comparison of case fatality rates of COVID-19/SARS-COV-2. Osong Public Health Res Perspect 2020; 11: 74.
24. Öztoprak F, Javed A. Case fatality rate estimation of COVID-19 for European countries: Turkey's current scenario amidst a global pandemic; comparison of outbreaks with European countries. EJMO 2020; 4: 149-59

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The effect of row number on clinical and life quality outcomes of patients who underwent arthroscopic rotator cuff repair

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ABSTRACT

Objective: Shoulder pain and disability are mostly seen following rotator cuff rupture. Arthroscopic rotator cuff repair becomes a gold standard treatment for rotator cuff rupture when conservative treatment fails. Comparing functional results, retear rates and reoperation rates of arthroscopic rotator cuff repair in terms of single-row versus double row techniques is our aim in this study.

Material and Method: Overall, 174 arthroscopic rotator cuff surgery patients were specified into 2 groups. Group 1 consists of 81 patients underwent single-row repair and group 2 consists of 93 patients consisted of transosseos equivalent technique double row. We evaluated demographic data and American Shoulder and Elbow Surgeons, Constant Murley, Visual analogue scale and 36-item Short Form subscale scores.

Results: Mean follow-up time was 14.08±4.77 months. ASES, CM and VAS following ARCR were similar between two groups. Some of SF-36 subscale score improvements after operation are significantly better in group 2; role limitations due to physical health (p=0.041), energy/fatigue (p=0.026), emotional well-being (p=0.017), pain (p=0.010), general health (p=0.037). Re-rupture rates were significantly different. In group 1 re-rupture rate was 13.6% and for group 2 it was 1.1% (p=0.001).

Conclusion: Lower re-rupture rates, and improved quality of life outcomes at short-term follow-up can be obtained by arthroscopic double-row repair. We suggest that the double-row technique can be considered for patients who have medium to large rotator cuff tears for lower re-rupture rates and some quality of life outcomes.

Keywords: Single-row repair , double-row repair, arthroscopy, rotator cuff rupture, supraspinatus

INTRODUCTION

Rotator cuff (RC) rupture is one of the most common causes of shoulder pain and disability (1). Although most ruptures are treated conservatively, many methods (especially arthroscopic) for tears requiring surgical intervention have been described in the last two decades. Nowadays arthroscopic rotator cuff repair (ARCR) becomes a gold standard treatment for RC rupture when conservative treatment fails (2).

Adequate fixation of the tendon to the footprint is important to achieve better tendon-bone healing (1). Many authors believe that the popularization and evolution of the arthroscopic technique was provided by the development of suture anchors however, proper placement of anchor sutures in the supraspinatus footprint at tuberculum majus of humerus is still a debate. During RC repair has not been clear yet (3). Single-row (SR) and double-row (DR) techniques are most preferred methods. Both SR and DR techniques are widely used in the treatment of RC ruptures and optimal treatment remains contraversial (4). Some of the biomechanical studies showed that DR repair provides stronger stability compared to SR repair (5), although some authors reported similar biomechanical strength and footprint coverage in cadaveric studies (6, 7). A recent systematic review evaluated meta-analyses about RC repair and most of the studies concluded that re-tear rates were less in DR repair but functional results were similar (8).

Retears after ARCR are not rare and retear rate reported up to 94% (9). Fortunately, most of the retears remain asymptomatic (10). Although some retears require further intervention and reoperations increase morbidity and treatment costs.

Our aim was to compare functional results, retear rates and reoperation rates of ARCR in terms of SR versus DR techniques.

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MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Kanuni Training and Research Hospital Clinical Researchs Ethics Committee (Date: 23.05.2021, Decision No: 2021/86). We retrospectively analysed the records of 208 patients who underwent arthroscopic RC repair between February 2017 and July 2019. Of these, 34 patients had a RC tear that could not be repaired (n=21) or had isolated subscapularis tendon repairs (n=13) and were excluded. This study has been performed due to the 1964 Declaration of Helsinki and its later updates.

The inclusion criteria were: age >18 years old; arthroscopic anterosuperior, superior, and/or posterosuperior RC tears, including those of the supraspinatus, infraspinatus and/or teres minor tendons; and a minimum 6 months follow-up, who has a fatty degeneration less than Goutallier grade 3 (11). Excluded patients were: those under the age of 18 years and more than 70 years old; those with a history of orthopaedic surgery on the same extremity, inflammatory arthropathy of same shoulder joint, concurrent pathology of the labrum that required repair, advanced osteoarthritis of the same glenohumeral joint, ipsilateral neurological deficit, chronic degenerative disease affecting the same shoulder joint, partial thickness and massive irreparable tears (11), and isolated subscapularis tendon tears. After all, 174 patients were available for the present study.

Information was obtained on age, gender, operated side, follow-up time, tear size, re-rupture rate and duration of operation. The classification of full-thickness cuff rupture was performed by assessing data acquired with magnetic resonance imaging (MRI). Tear classification was made according to the DeOrio and Cofield classification, with the size of full-thickness tears of <1 cm considered small, 1-3 cm considered medium, 3-5 cm considered large, and > 5 cm considered massive (12).

Two different surgeon's patients' were assessed as two groups. One surgeon perfoms single-row in his clinical practice and, other one performs double-row for arthroscopic supraspinatus tendon repair. Patients were specified into 2 groups according to row number. Group 1 consists of patients underwent SR repair (**Figure 1**) and group 2 consists of transosseos equvalent technique (TOE) DR (**Figure 2**).

The patients were subjected to a follow-up examination by an independent observer. For the functional and quality of life evaluation of patients, pre- and postoperative American Shoulder and Elbow Surgeons (ASES) scores (13), Constant-Murley (CM) scores (14), Visual analogue scale (VAS) (15) and 36-item Short Form Health Survey (SF-36) (16) scores were evaluated.

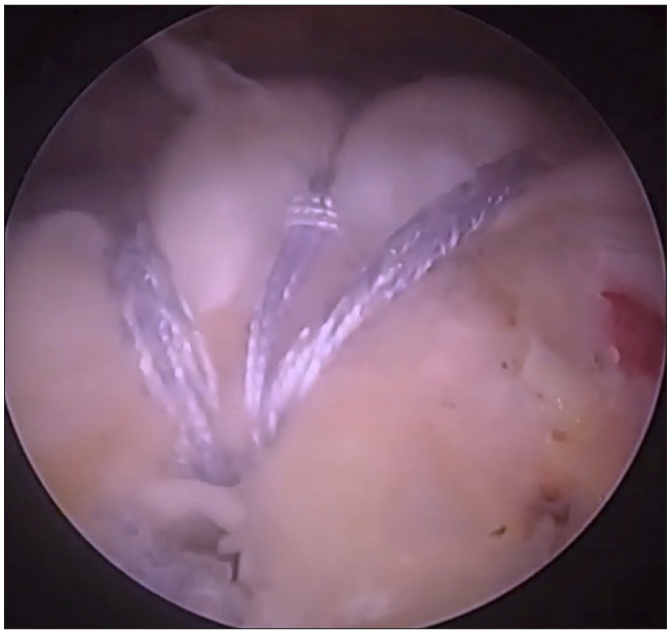

Figure 1. A patient in group 1 who underwent single row rotator cuff repair

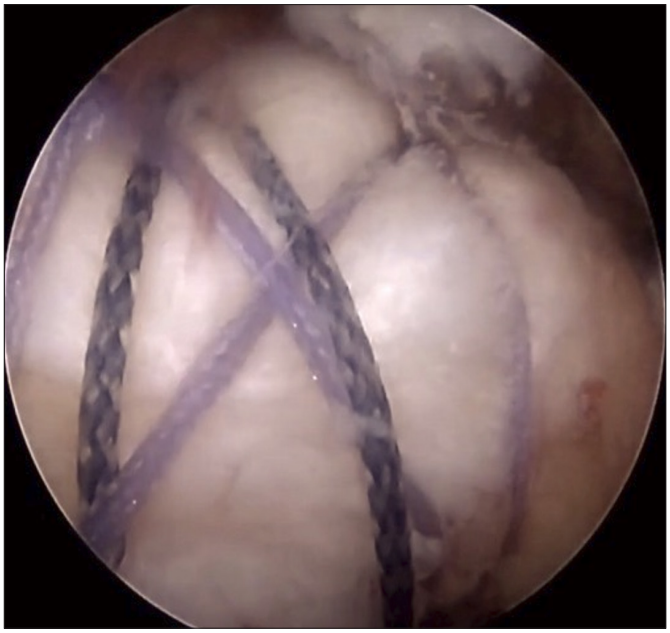

Figure 2. A patient in group 2 who underwent double row rotator cuff repair

Surgical Technique

After performing general anesthesia patients were taken to beach chair position. Standard posterior portal was used to evaluate the glenohumeral joint, supraspinatus, subscapularis and long head of the biceps tendon. Biceps tenotomy was performed in all patients independent from the age. All patients received subacromial decompression, routine acromioplasty was not performed. The suture configuration and repair technique were determined by surgeon's choice.

In patients who received single row repair, one or two metal 5.5mm suture anchors double loaded with number

2 ethibond sutures (Ethicon, Johnson & Johnson, Norwood, MA). The number of sutures determined by tear size. Anchors were inserted to 2 mm lateral to the head of humerus. Each suture were passed the tendon from lateral to the musculotendinious junction to make horizontal matress configration. Samsung medical center (SMC) knot was used to fix tendon over the footprint.

In patients who underwent TOE repair, previously described procedures were completed. Firstly medial row was tied and, the suture limbs were crossed. By this method suture bridges were created across the tendon. One or two footprint anchors were inserted to the lateral aspect of the greater tuberosity for completing the lateral row.

Same postoperative rehabilitation program was prescribed to all patients. Shoulder sling was used for first four weeks, pendulum exercises were started immediately. Active shoulder motion was allowed after four weeks. Streching was contraindicated for three months.

Statistical Analysis

The mean, standard deviation, and percent values were used, as appropriate, to describe the data. The distribution for each measured variable was evaluated for normality using the Kolmogorov–Smirnov test. Categorical variables are summarized as frequency (n) and a percent of the total. Statistical analyses were conducted with $\chi 2$ test test to compare categorical variables (gender, injured side, tear size and re-rupture) and the Student t test to analyze between group differences in preoperative and postoperative ASES Subjective Shoulder Scale, CM, VAS and SF-36 subscales to compare the number of suture anchors used between the 2 groups. Tear size and gender categoric variables on clinical score improvements were analysed by one way ANOVA and Post-Hoc tests. All statistical analyses were performed using the SPSS v24 (SPSS Inc., Armonk, NY) software. P values <0.05 were considered to be statistically significant.

RESULTS

The general patient demographics and disease-specific characteristics of the patients were presented in **Table 1**. When compared to the group 1, group 2 had a significantly lower re-rupture (p=0.001) and surgery time (p=0.043).

Table 2 presents the preoperative and postoperative ASES, CM, VAS, and SF-36 subscale scores at final examination for all patients. Also mean differences of these scores were defined. All values of ASES and CM scores are not significantly different between two groups. Some of SF-36 subscale score improvements after operation are significant; role limitations due to physical health (p=0.041), energy/fatigue (p=0.026), emotional well-being (P=0.017), pain (p=0.010), general health (p=0.037).

Table 3 shows the relationship between gender and clinical score improvements following surgery. Some of the SF-36 subscales were significantly different between genders. Tear size and clinical score improvements were significantly related in terms of CM and physical functioning subscales of SF-36. There was no significant correlation between

Table 1. Demographic and disease-specific characteristics of the patients

Variable	Entire Study Population	Group 1 (n=81)	Group 2 (n=93)	p
Patient number	174 (100)	81 (46.6)	93 (53.4)	
Age, year	62.48±6.43	62.77±5.75	62.22±6.99	0.574
Gender				0.704
Female	110 (63.2)	50 (61.7)	60 (64.5)	
Male	64 (36.8)	31 (38.3)	33 (35.5)	
Injured side				0.863
Right	89 (51.1)	42 (51.9)	47 (50.5)	
Left	85 (48.9)	39 (48.1)	46 (49.5)	
Tear size				0.684
Small	45 (25.9)	22 (27.2)	23 (24.7)	
Medium	94 (54)	41 (50.6)	53 (57)	
Large	35 (20.1)	18 (22.2)	17 (18.3)	
Follow-up time, months	14.08±4.77	14.03±4.89	14.11±4.69	0.911
Re-rupture				0.001
Yes	12 (6.9)	11 (13.6)	1 (1.1)	
No	162 (93.1)	70 (86.4)	92 (98.9)	
Surgery time, minutes, SD	74.82±14.58	72.74±13.72	77.22±15.24	0.043

Abbreviations: statistically significant p values were defined as bold style.

Table 2. Preoperative, postoperative and mean change of clinical scores compared between two groups

Clinical Score	All patients	Group 1 (n=81)	Group 2 (n=93)	p
ASES				
Preoperative	41.85±7.10	40.90±7.91	42.68±6.22	0.098
Postoperative	77.25±12.01	75.35±14.66	78.90±8.85	0.052
Difference	35.39±9.78	34.45±11.40	36.21±8.09	0.238
CM				
Preoperative	40.98±5.22	40.69±5.47	41.24±5.02	0.486
Postoperative	76.75±11.80	75.23±14.03	78.07±9.31	0.113
Difference	35.76±10.64	34.54±12.11	36.82±9.10	0.158
VAS				
Preoperative	6.21±0.89	6.32±0.89	6.08±0.81	0.436
Postoperative	2.03±1.32	2.03±1.46	2.04±1.38	0.313
Difference	4.15±1.65	4.29±1.47	4.03±1.32	0.658
SF-36				
Physical functioning				
Preoperative	59.48±8.83	57.77±8.62	60.96±8.79	0.017
Postoperative	84.19±11.01	82.65±12.27	85.53±9.65	0.085
Difference	24.71±9.65	24.87±10.81	24.56±8.58	0.835
Role limitations due to physical health				
Preoperative	18.41±17.04	18.27±14.40	18.54±19.11	0.915
Postoperative	73.99±15.75	70.06±16.01	77.41±14.77	0.002
Difference	55.57±22.87	51.79±23.38	58.87±22.00	0.041
Role limitations due to emotional problems				
Preoperative	40.48±27.69	36.34±28.10	44.08±26.97	0.066
Postoperative	85.58±18.98	83.70±20.73	87.21±17.26	0.225
Difference	45.09±27.56	47.35±25.81	43.12±29.00	0.314
Energy/fatigue				
Preoperative	29.79±11.16	30.43±11.24	29.24±11.13	0.487
Postoperative	74.45±14.30	71.66±15.85	76.88±12.39	0.016
Difference	44.65±18.93	41.23±20.77	47.63±16.72	0.026
Emotional well-being				
Preoperative	33.37±11.76	32.34±12.65	34.27±10.92	0.281
Postoperative	66.41±17.38	62.32±18.24	69.97±15.85	0.003
Difference	33.03±15.82	29.97±16.00	35.69±15.26	0.017
Social functioning				
Preoperative	28.25±10.61	26.80±10.07	29.52±10.95	0.091
Postoperative	109.05±149.45	94.60±117.63	121.63±172.11	0.235
Difference	43.96±14.28	42.82±14.87	44.95±13.75	0.328
Pain				
Preoperative	23.02±10.09	22.27±10.81	23.67±9.43	0.361
Postoperative	73.63±20.86	69.12±23.40	77.55±17.58	0.007
Difference	50.60±17.99	46.85±19.42	53.88±16.05	0.010
General health				
Preoperative	28.04±13.33	27.28±13.73	28.70±13.01	0.484
Postoperative	75.45±15.99	71.79±18.30	78.65±12.94	0.004
Difference	47.41±17.21	44,50±18.48	49.94±15.69	0.037
Health change				
Preoperative	19.25±16.21	16.66±13.69	21.50±17.90	0.049
Postoperative	79.45±18.37	76.54±20.67	81.98±15.79	0.051
Difference	60.20±23.12	59.87±24.26	60.48±22.21	0.863

ASES American Shoulder and Elbow Surgeons Score, CM Constant Murley score, VAS Visual analogue scale, SF-36 36-item Short Form Health Survey, statistically significant p values were defined as bold style.

Table 3. Comparing results of tear size and gender with clinical scores

Clinical score improvement	Gender			Tear Size			
	Female (n=110)	Male (n=64)	p	Small (n=45)	Medium (n=94)	Large (n=35)	P Post-Hoc Analysis
ASES	34.77±11.17	36.46±6.72	0.272	36.20±7.35	36.13±9.19	32.37±13.20	S-M: 0.999 M-L: 0.126 S-L: 0.191
CM	35.30±11.85	36.54±8.17	0.461	38.48±7.40	36.56±10.04	30.11±13.60	S-M: 0.557 M-L: 0.005 S-L: 0.001
VAS	4.29±1.47	4.03±1.32	0.194	4.39±1.57	4.29±1.12	4.03±1.32	S-M: 0.235 M-L: 0.456 S-L: 0.298
SF-36							
Physical functioning	23.31±9.79	27.10±8.98	0.012	27.33±7.87	25.15±9.54	20.14±10.67	S-M: 0.410 M-L: 0.021 S-L: 0.002
Role limitations due to physical health	51.31±22.73	62.89±21.35	0.001	56.66±17.99	55.00±24.54	55.71±24.31	S-M: 0.916 M-L: 0.987 S-L: 0.982
Role limitations due to emotional problems	42.11±28.54	50.21±25.20	0.061	44.53±29.37	43.03±28.04	51.37±23.38	S-M: 0.951 M-L: 0.280 S-L: 0.514
Energy/fatigue	40.90±19.39	51.09±16.34	0.001	49.00±18.35	44.46±18.29	39.57±20.52	S-M: 0.380 M-L: 0.388 S-L: 0.069
Emotional well-being	32.03±15.91	34.75±15.66	0.277	37.06±14.60	31.36±16.13	32.34±16.04	S-M: 0.115 M-L: 0.947 S-L: 0.379
Social functioning	41.72±14.33	47.81±13.45	0.006	44.37±10.80	43.03±15.15	45.94±15.88	S-M: 0.862 M-L: 0.561 S-L: 0.879
Pain	46.96±18.49	56.87±15.33	< 0.001	55.37±14.44	49.56±18.50	47.28±19.93	S-M: 0.174 M-L: 0.796 S-L: 0.113
General health	44.95±17.65	51.64±15.68	0.013	51.00±12.64	46.64±18.17	44.85±19.30	S-M: 0.344 M-L: 0.858 S-L: 0.254
Health change	56.59±23.13	66.40±21.92	0.007	65.55±22.16	59.57±23.50	55.00±22.52	S-M: 0.325 M-L: 0.574 S-L: 0.106

ASES American Shoulder and Elbow Surgeons Score, CM Constant Murley score, VAS Visual analogue scale, SF-36 36-item Short Form Health Survey, statistically significant p values were defined as bold style.

side, follow-up time and clinical scores.

DISCUSSION

This study reported that, DR repair technique was shown to be significantly associated higher with some of SF-36 (role limitations due to physical health, energy/fatigue, emotional well-being, pain, general health) scores and lower re-rupture rates compared with single row repair technique of an arthroscopic RC repair. ASES and CM scores showed no significant difference between two surgical techniques.

Biomechanical advantages of DR compared with SR have been reported by numeruous studies before (17, 18). Kim et al. (17) reported that cyclic loads following DR repair made lower gap formation compared with SR repair at rotator cuff. The results of another study showed that, more than twice of the native rotator cuff footprint coverage was obtained with DR compared to SR (19). Nevertheless, higher traction strength after DR repair was reported compared to SR repair with cadaveric biomechanical study by Ma et al. (20). These biomechanical advantages appear clinically as re-rupture probability to happen.

Tudisco et al. analysed 20 SR and 20 DR patients with 3 tesla MRI and reported 25% re-rupture in DR patients and 60% re-rupture in SR patients with mean 40 months follow-up. Our results show that SR repaired patients 13.6% had re-rupture and DR patients had 1.1% re-rupture. We did not use MRI for re-rupture investigation, only assessed for symptomatic re-ruptures so our rates were less. Nevertheless, the fact that our results confirmed that we can obtain less re-rupture rates with DR repair method compared with SR method.

Many previous studies compared clinical outcomes of SR and DR repair techniques for ARCR and reported no difference (21-24). Franceschi et al reported that

at the 2-year follow-up of 30 SR and 30 DR patients, University of California, Los Angeles (UCLA) score and range of motion values were not statistically different (23). Sugaya et al (25) followed up 78 patients' mean 35 months and reported no significant difference between SR and DR techniques in terms of ASES and UCLA scores, however they reported better structural outcome of dual-row repairs than the SR technique. However, a majority of these studies were from the patients aged around 65 years. Although, a study included younger patients who are generally <50 years, no superiority of clinical outcomes between SR and DR groups were reported (26). Our results showed no difference between groups in terms of ASES and CM scores. Some of SF-36 subscales were found higher in DR group. Our findings are parallel with previous studies except the quality of life results. This difference may be due to our short follow-up duration. Longer follow-up time may make quality of life scores similar between two groups.

Parallel with previous studies, Saradakis et al. (27) concluded that there is no statistically significant difference between SR and DR in terms of ASES, CM and UCLA clinical scores. Despite that, a significant difference was observed for larger ruptures (>3.0 cm). In another meta-analysis, SR and DR outcomes were similar and larger rupture size worsen the outcomes (10). Senna et al reported similar results with previous studies (1). Our study showed that both groups had similar clinical outcomes, even though only large tears were analysed and no significant differences were detected between both groups except some of SF-36 subscales.

After ARCR, rehabilitation protocols may effect tendon healing. A recent randomized controlled trial reported that, decreased shoulder stiffness and lower re-rupture risk can be obtained with DR repair and accelerated rehabilitation(22). This is particularly relevant for young, active patients who require early return to work and given that young age is a risk factor for postoperative stiffness after rotator cuff repair (28) However, the (add) same postoperative rehabilitation protocol was applied to all patients in our study.

This study showed that, tendon healing and clinical outcomes at short-term appear to be acceptable for both techniques. We found lower re-rupture rates with DR technique and patients with high functional demand may be suitable for DR repair for less complication. The DR repair technique, which is currently known to provide a potentially superior healing environment, can be chosen for younger or active older patients.

The gender distribution between two groups were not statistically different. All clinical scores were also not different in terms of gender. Previous studies promote these findings (29). Grasso et al. reported no difference between groups in terms of gender. Although pain perception can differ between genders, this was not supported by both previous studies and our study.

Limitations are present in our study. First, the mean follow-up time of 14 months is short for the prediction of long-term outcomes. However, given the good and excellent clinical outcomes after both DR repair and SR repair, we think that it is possible to obtain good-excellent long-lasting clinical outcomes with both techniques. Also, lower re-rupture rates following DR technique, we think that good long-lasting tendon integrity can be provided by DR repair. Second, there might be no objective randomization and biases might affect the outcomes.

CONCLUSION

Lower re-rupture rates, and improved quality of life outcomes at short-term follow-up can be obtained by arthroscopic double-row repair. We suggest that the double-row technique can be considered for patients who have medium to large rotator cuff tears, active and high functional demand.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Kanuni Training and Research Hospital Clinical Researchs Ethics Committee (Date: 23.05.2021, Decision No: 2021/86).

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. Senna LF, Ramos MRF, Bergamaschi RF. Arthroscopic rotator cuff repair: single-row vs. double-row - clinical results after one to four years. Rev Bras Ortop 2018; 53: 448-53.
2. Aydin N, Karaismailoglu B, Gurcan M, Ozsahin MK. Arthroscopic double-row rotator cuff repair: a comprehensive review of the literature. Sicot j 2018; 4: 57.
3. Spiegl UJ, Euler SA, Millett PJ, Hepp P. Summary of meta-analyses dealing with single-row versus double-row repair techniques for rotator cuff tears. Open Orthop J 2016; 10: 330-8.
4. Huang AL, Thavorn K, van Katwyk S, MacDonald P, Lapner P.

Double-row arthroscopic rotator cuff repair is more cost-effective than single-row repair. J Bone Joint Surg Am 2017; 99: 1730-6.

5. Hohmann E, König A, Kat CJ, Glatt V, Tetsworth K, Keough N. Single- versus double-row repair for full-thickness rotator cuff tears using suture anchors. A systematic review and meta-analysis of basic biomechanical studies. Eur J Orthop Surg Traumatol 2018; 28: 859-68.
6. Meisel AF, Henninger HB, Barber FA, Getelman MH. Biomechanical comparison of standard and linked single-row rotator cuff repairs in a human cadaver model. Arthroscopy 2017; 33: 938-44.
7. Simmer Filho J, Voss A, Pauzenberger L, et al. Footprint coverage comparison between knotted and knotless techniques in a single-row rotator cuff repair: biomechanical analysis. BMC Musculoskelet Disord 2019; 20: 123.
8. Hurley ET, Maye AB, Mullett H. Arthroscopic rotator cuff repair: a systematic review of overlapping meta-analyses. JBJS Rev 2019; 7: e1.
9. Galatz LM, Ball CM, Teefey SA, Middleton WD, Yamaguchi K. The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. J Bone Joint Surg Am 2004; 86: 219-24.
10. Millett PJ, Warth RJ, Dornan GJ, Lee JT, Spiegl UJ. Clinical and structural outcomes after arthroscopic single-row versus double-row rotator cuff repair: a systematic review and meta-analysis of level I randomized clinical trials. J Shoulder Elbow Surg 2014; 23: 586-97.
11. Sahoo S, Ricchetti ET, Zajichek A, et al. Associations of preoperative patient mental health and sociodemographic and clinical characteristics with baseline pain, function, and satisfaction in patients undergoing rotator cuff repairs. Am J Sports Med 2020; 48: 432-43.
12. 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.
13. Richards RR, An KN, Bigliani LU, et al. A standardized method for the assessment of shoulder function. J Shoulder Elbow Surg 1994; 3: 347-52.
14. Constant CR, Murley AH. A clinical method of functional assessment of the shoulder. Clin Orthop Relat Res 1987; 214: 160-4.
15. Boonstra AM, Schiphorst Preuper HR, Reneman MF, Posthumus JB, Stewart RE. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. Int J Rehabil Res 2008; 31: 165-9.
16. Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in orthopaedics: a brief guide. J Bone Joint Surg Am 2015; 97: 1628-34.
17. Kim DH, Elattrache NS, Tibone JE, et al. Biomechanical comparison of a single-row versus double-row suture anchor technique for rotator cuff repair. Am J Sports Med 2006; 34: 407-14.
18. Smith CD, Alexander S, Hill AM, et al. A biomechanical comparison of single and double-row fixation in arthroscopic rotator cuff repair. J Bone Joint Surg Am 2006; 88: 2425-31.
19. Brady PC, Arrigoni P, Burkhart SS. Evaluation of residual rotator cuff defects after in vivo single- versus double-row rotator cuff repairs. Arthroscopy 2006; 22: 1070-5.
20. Ma CB, Comerford L, Wilson J, Puttlitz CM. Biomechanical evaluation of arthroscopic rotator cuff repairs: double-row compared with single-row fixation. J Bone Joint Surg Am 2006; 88: 403-10.
21. Charousset C, Grimberg J, Duranthon LD, Bellaiche L, Petrover D. Can a double-row anchorage technique improve tendon healing in arthroscopic rotator cuff repair?: A prospective, nonrandomized, comparative study of double-row and single-row anchorage techniques with computed tomographic arthrography tendon healing assessment. Am J Sports Med 2007; 35: 1247-53.
22. Franceschi F, Papalia R, Franceschetti E, et al. Double-Row Repair Lowers the Retear Risk After Accelerated Rehabilitation. Am J Sports Med 2016; 44: 948-56.
23. Franceschi F, Ruzzini L, Longo UG, et al. Equivalent clinical results of arthroscopic single-row and double-row suture anchor repair for rotator cuff tears: a randomized controlled trial. Am J Sports Med 2007; 35: 1254-60.
24. Nicholas SJ, Lee SJ, Mullaney MJ, et al. Functional outcomes after double-row versus single-row rotator cuff repair: a prospective randomized trial. Orthop J Sports Med 2016; 4: 2325967116667398.
25. Sugaya H, Maeda K, Matsuki K, Moriishi J. Functional and structural outcome after arthroscopic full-thickness rotator cuff repair: single-row versus dual-row fixation. Arthroscopy 2005; 21: 1307-16.
26. Hantes ME, Ono Y, Raoulis VA, et al. Arthroscopic single-row versus double-row suture bridge technique for rotator cuff tears in patients younger than 55 years: a prospective comparative study. Am J Sports Med 2018; 46: 116-21.
27. Saridakis P, Jones G. Outcomes of single-row and double-row arthroscopic rotator cuff repair: a systematic review. J Bone Joint Surg Am 2010; 92: 732-42.
28. Tashjian RZ, Hollins AM, Kim HM, et al. Factors affecting healing rates after arthroscopic double-row rotator cuff repair. Am J Sports Med 2010; 38: 2435-42.
29. Grasso A, Milano G, Salvatore M, Falcone G, Deriu L, Fabbriciani C. Single-row versus double-row arthroscopic rotator cuff repair: a prospective randomized clinical study. Arthroscopy 2009; 25: 4-12.

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Direct cost analysis for patients with severe asthma receiving omalizumab treatment

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ABSTRACT

Aim: The present study aims to reveal a direct cost analysis of patients with severe allergic asthma receiving omalizumab treatment.

Material and Method: Twenty-two adults with severe allergic asthma who were treated with omalizumab and were routinely checked on the 16th week, 1st year, and 3rd year of treatment were included in the study. Clinical and demographic features of subjects were retrospectively documented before and after omalizumab treatment as well as pharmaceutical, emergency and hospital costs.

Results: The monthly treatment cost per patient was higher during the 16th week, 1st year, and 3rd year (€411.80±190.84, €409.7±211.57, €404.2±157.30 respectively) when compared with the pre-treatment period (€107.91±48.62) ($p<0.001$). Similarly, monthly emergency visit cost per patient at 16thweek, 1st year, and 3rd year of omalizumab treatment (€0.03±0.13, €0.19±0.51, €0.56±0.41 respectively), as well as the monthly hospitalization cost per patient at 16th week, 1st year, and 3rd year of omalizumab treatment (€1.44±5.57, €1.50±5.27, €16.3±13.8 respectively) were both lower compared to pre-treatment period (€1.82±1.23 and €17.69±10.84 respectively) ($p<0.001$ for both). A statistically significant drop was observed in the frequency of asthma exacerbations as well as emergency visits, hospitalizations and number of patients receiving systemic corticosteroid with omalizumab treatment. An improvement was also detected in asthma control test scores, forced expiratory volume in 1 second, and peak expiratory flow values of patients compared to the baseline values.

Conclusion: Omalizumab treatment is clinically effective and although it adds an extra pharmaceutical cost to the patients' management it reduces the emergency and hospital costs.

Keywords: Asthma management, severe asthma, cost analysis, omalizumab

INTRODUCTION

Asthma is a serious community health problem that affects 200-300 million individuals worldwide (1,2) and causes approximately 250,000 deaths annually (3). Severe asthma accounts for 5-10% of all asthma cases (4). From the perspective of the usage of health services, it is known that severe asthma opens the gateway to higher medication costs, an increased rate of emergency visits, and a higher rate of hospitalization compared to cases involving mild or moderate asthma (5). This indicates that there is a link between the severity of asthma and serious financial problems for patients (6).

A limited number of Turkish studies have shown that as the severity of asthma increases, relevant costs increase. Çelik et al. (7) found that the direct annual cost of asthma was about $1,465 per patient, while the direct annual cost of severe asthma was about $3,491 per patient. Bavbek et al. found that the annual cost per patient with uncontrolled asthma was more than twice the annual cost per patient with controlled asthma (8). In the same study, the authors showed that the cost varied greatly depending on the attack severity (mild attack: €128.60, moderate attack: €172.60, severe attack: €308.20)(8). As discussed above, severe asthma is a clinical condition that causes a considerable increase in cost, poorer quality of life, loss of productivity at work, and a decreased number of attack-free periods. For these reasons, new agents have been introduced for the treatment of severe asthma, one of which is omalizumab.

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Omalizumab is a humanized recombinant DNA derivative as well as a human IgG1k monoclonal antibody that specifically binds free IgE in blood and interstitial fluid (9). Omalizumab treatment was licensed in Turkey in 2008 for the management of severe allergic asthmatics patients if disease control is not achieved despite high-dose inhaled corticosteroid treatment. Clinical studies and real-life data show that omalizumab leads to a significant reduction in asthma attacks, unplanned physician visits, emergency visits, and hospitalizations as well as a significant increase in quality of life for patients with severe asthma (10-15).

While there is a limited number of studies investigating the cost-effectiveness of omalizumab, they have revealed contradictory results. Omalizumab was not found to be cost-effective in one study hailing from Canada (16), whereas it was found to be cost-effective in another study hailing from Brazil (17). However, as of yet there is no Turkish-based studies regarding cost analysis of omalizumab. The present study aims to reveal treatment costs as well as clinical parameters in severe allergic asthmatics before and after omalizumab treatment.

MATERIAL AND METHOD

This study was approved by Ankara Keçiören Training and Research Hospital Clinical Researchs Ethics Committee (Date: 12.27. 2017, Decision:1553). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population and Design

This retrospective study was planned in the allergy and immunology clinic at Atatürk Chest Disease and Chest Surgery Training and Research Hospital between January 1st–and April 1st, 2018. Adults with severe allergic asthma who have treated with omalizumab after a follow-up for at least one year in our clinic between 2008 and 2015 were included in the study. Patients with missing data regarding spirometric values, asthma control test (ACT) scores, record of asthma exacerbations, emergency visits and hospitalizations in hospital files were excluded from the study.

Patients' demographic characteristics, comorbid conditions, atopy status, omalizumab dose, administration interval, pre- and post-treatment (16th week, 1st year, and 3rd year) forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF) and FEV_1/FVC (forced vital capacity) values, ACT scores, number of asthma attacks, number of emergency visits, number of hospitalizations, medications and drug doses were recorded from their patients' files.

Omalizumab Administration Protocol

Omalizumab is administered in subjects with asthma if disease control was not achieved with high-dose inhaled corticosteroid plus long-acting beta2 agonist and/or leukotriene receptor antagonists, with a skin test or specific IgE positivity to at least one perennial allergen (house dust mite, cat-dog hair, cockroaches or mold spores) and with a total serum IgE level between 30–1500 IU/mL. Omalizumab treatment was administered subcutaneously every two or four weeks with doses and dosing frequencies determined according to baseline serum total IgE level and body weight (18). At 16th week after commencing treatment clinical response was evaluated according to symptoms, reliever drug use, frequency of exacerbations and asthma control (10). The treatment is maintained with the same dose in patients who benefit from the treatment, and is terminated in patients who do not.

Evaluation of the Cost

The cost of all medications used by the patients before and after treatment (including omalizumab) was specified as the 'direct medical cost'. The average amount invoiced in cases where the patient had visited the emergency room and was hospitalized due to asthma was calculated based on the current cost information received from the accounting department within our hospital. The 'hospitalization cost' was calculated as the hospital cost+the pharmacy cost. The 'total cost' was calculated as being the direct medical cost+the total emergency room cost+the total hospitalization cost. All costs were calculated as being the total monthly cost and monthly cost per patient. The medical costs (medications regularly used by the patient and omalizumab) and hospital costs were calculated based on the pricing stipulated in the Turkish Social Security Institution's Communique on Medical Practices. The costs as calculated in Turkish Liras (TRY) were converted to Euros using the mid-term exchange rate in 2018, which was TRY 5.66.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, USA) was used for statistical assessments. The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. Values with a normal distribution were presented as being the mean±standard deviation and values without normal distribution were presented as being the median (min-max). Categorical variables were presented as numbers and percentages. The differences between pre- and post-treatment follow-ups were evaluated using the mixed model analysis in repeating samples. $P<0.05$ was considered to be statistically significant in the statistical analysis.

RESULTS

Table 1 shows the demographic characteristics of the patients. The study population consisted of 22 patients, including 12 (54.5%) males and 10 (45.5%) females.

72.7% of the patients had rhinitis-nasal polyposis, 13.6% had drug allergies, 77.3% were sensitive to house dust mites, 22.7% were sensitive to cat-dog hair, 45.5% were sensitive to mold, 22.7% were sensitive to cockroaches, and %22.7 were sensitive to pollen.

The average pre-treatment body weight among the patients was 81.6±16.2 kg (min-max: 49-110), and the median total IgE was 218 IU/ml (min-max: 31-990). The median omalizumab dose was 300 mg (min-max: 150-600) and the median monthly total omalizumab dose was 375 mg (min-max: 150-1200).

Table 1. Demographic and clinical findings of patients

Variables	n (%)
Gender	
Male	12 (54.5)
Female	10 (45.5)
Rhinitis-nasal polyp	16 (72.7)
Drug allergy	3 (13.6)
Urticaria angioedema	1 (4.5)
Other	
Anemia+OSAS	1 (4.5)
Hypertension	1 (4.5)
Hypertension+OSAS	1 (4.5)
Chronic sinusitis	2 (9.1)
Latex allergy	1 (4.5)
Obesity	1 (4.5)
OSAS	2 (9.1)
Osteoporosis+Thrombocytopenia	1 (4.5)
Reflux	1 (4.5)
Reflux+Hypertension	1 (4.5)
Reflux+Hypertension+ OSAS	1 (4.5)
Reflux+Venous insufficiency	1 (4.5)
Ulcer	1 (4.5)
House dust mite sensitization	17 (77.3)
Cat-dog sensitization	5 (22.7)
Mold sensitization	10 (45.5)
Cockroach sensitization	5 (22.7)
Pollen sensitization	5 (22.7)

Categorical variables were shown as number (%).
Abbreviations: OSAS: Obstructive sleep apnea syndrome

While the average post-treatment FEV_1(%) level, PEF(%) level, and ACT scores of the patients were significantly higher compared to the pre-treatment period (p=0.005, p=0.003, and p<0.001 respectively), they did not show a significant difference between follow-ups (16th week, 1st year, and 3rd year). There was no significant difference between any of the follow-ups before or after the treatment in terms of the average FEV_1 (ml), average PEF (ml), and average FEV_1/FVC ratio (**Table 2**).

Table 3 shows the change in the number of attacks, emergency visits, hospitalizations, and cost distribution between the pre- and post-treatment period in detail.

The average cost of emergency visits per patient was lower in all of post-treatment follow-ups compared to the pre-treatment period, while it was higher in the 3rd year compared to the 16th week and the 1st year (p<0.001). The average total hospitalization cost per patient among those who were hospitalized was lower in the 16th week and 1st year compared to the pre-treatment period (p<0.001), while no significant difference was found between the 3rd year and the pre-treatment period. The average total pre-treatment cost of the patients was found to be significantly lower compared to the average total post-treatment cost (p<0.001). Despite this, no significant difference between the post-treatment follow-up periods (16th week, 1st year, and 3rd year) in terms of the average total cost was found (**Figure**).

Figure. Cost diagram before and after treatment

Table 2. Changes in pulmonary function tests and asthma control before and after Omalizumab treatment

Variables	Pre-treatment n=22	16th week n=22	First year n=22	Third year n=17	p
FEV_1 (%)	69.5±18.8	82.5±18.3	83±19.6	78.6±22.4	0.005*
FEV_1 (ml)	2286.4±743.5	2535.9±865.9	2525.5±824.9	2245.9±891.1	0.306
PEF (%)	71.2±23.3	81.4±23.5	83.1±24.7	80.2±25.9	0.003*
PEF (ml)	5745±1994.6	6256.4±2238.2	6192.3±2016.7	5652.9±2345.7	0.209
FEV_1/FVC ratio	76.5±7.8	80.3±6.7	80±11.3	75.6±10.2	0.327
ACT (score)	11.4±2.9	22±2.2	22.2±3.2	22.3±4.6	<0.001*

Normally distributed numerical variables were shown as mean±standard deviation. * p<0.05 shows statistical significance.
Abbreviations: FEV_1: Forced expiratory volume in 1 second, PEF: Peak expiratory flow, FVC: Forced vital capacity, ACT: Asthma control test

Table 3. The number of attacks, emergency room admissions, hospitalization and cost distribution of the patients compared to the pre and post treatment period.

Variables	Pre-treatment n=22	16th week n=22	First year n=22	Third year n=17	p
Direct medical cost (€)	1900.13	9026.99	8999.13	6591.24	
Average cost per person (€)	86.37±30.44	410.31±268.30	409.05±267.40	387.7±194.53	<0.001*
Number of patients suffering from attack, n(%)	13 (59.1)	3 (13.6)	6 (27.3)	10 (58.8)	0.007*
Total number of attacks (n)	37	3	8	24	-
Average number of attacks per person (n)	2.0±1.7	0.1±0.4	0.4±0.7	1.5±1.4	0.001*
Number of patients admitted to emergency, n (%)	8 (36.4)	1 (4.5)	4 (18.1)	7 (41.2)	0.020*
Total number of emergency applications (n)	20	1	4	15	-
Average number of emergency applications per person (n)	2.5±1.9	0.1±0.2	0.2±0.5	1.1±1.0	0.003*
Total Emergency cost (€)	40.09	0.61	3.89	10.95	-
Average Emergency cost per person (€)	1.82±1.23	0.03±0.13	0.19±0.51	0.56±0.41	<0.001*
Number of hospitalized patients, n(%)	11 (50.0)	2 (9.1)	3 (13.6)	5 (29.4)	<0.001*
Total number of hospitalizations (n)	17	2	3	11	-
Average number of hospitalizations per person (n)	1.6±0.8	0.1±0.3	0.1±0.4	0.8±1.0	<0.001*
Total hospital cost (€)	307.85	27.04	24.10	215.60	-
Average cost of hospital per person (€)	14.0±8.75	1.23±4.62	1.09±3.72	10.4±9.1	<0.001*
Total Pharmacy costs (€)	81.39	4.57	8.92	118.14	-
Average pharmacy cost per person (€)	3.70±2.59	0.21±0.98	0.41±1.60	5.8±4.9	<0.001*
Total hospitalization cost (€)	389.30	31.61	33.02	333.74	-
Average total hospitalization cost per person (€)	17.69±10.84	1.44±5.57	1.50±5.27	16.3±13.8	<0.001*
Total cost per person (€)	107.91±48.62	411.80±190.84	409.7±211.57	404.2±157.30	<0.001*

Normally distributed numerical variables were shown as mean±standard deviation. Numerical variables that do not show normal distribution were shown with median (min-max). Categorical variables were shown as number (%). * p <0.05 shows statistical significance.

There was a significant decrease in the rate of patients experiencing attacks in the 16th (13.6%) and the 1st year (27.3%) compared to the pre-treatment period (59.1%). Moreover, there was a significant increase in the rate of patients experiencing attacks in the 3rd year (58.8%) compared to the 16th week and the 1st year and it was similar to the rate of patients experiencing attacks in the pre-treatment period (p=0.007). While the average number of attacks among these patients showed a significant difference in the 16th week and the 1st year post-treatment (p=0.001), it was similar in the 3rd year post-treatment and the pre-treatment period.

There was a significant decrease in the rate of patients visiting emergency room in the 16th week (4.5%) and the 1st year (18.1%) post-treatment compared to the pre-treatment period (36.4%). The average number of emergency room visits among these patients was lower in all post-treatment follow-ups compared to the pre-treatment period (p=0.003).

There was a significant decrease in the rate of hospitalization in all post-treatment follow-ups compared to the pre-treatment period. While there was a significant increase in the rate of hospitalization in the 3rd year compared to the 16th week and the 1st year post-treatment, it was lower compared to the pre-treatment period (p<0.001). The average number of hospitalizations among these patients was lower in all of the post-treatment follow-up periods compared to the pre-treatment period. Even though omalizumab use led to a significant increase in medical cost, the number of attacks did decrease by 91.9% in the 16th week, 78.4% in the 1st year, and 35.1% in the 3rd year post-treatment compared to the pre-treatment period. The number of emergency room visits decreased by 95% in the 16th week, 80% in the 1st year and 25% in the 3rd year post-treatment compared to the pre-treatment period. The number of hospitalizations decreased by 88.2% in the 16th week post-treatment, 82.3% in the 1st year post-treatment, and 35.3% in the 3rd year post-treatment compared to the pre-treatment period.

The ratio of the patients receiving systemic steroid therapy was at its highest before treatment, it was found to significantly decrease in the 16th week and the 1st year, and to increase in the 3rd year compared to the 16th week and the 1st year; however, it still was significantly lower compared to the pre-treatment period (p<0.001). Median systemic steroid dose was not significantly different in 16th week, 1st year, and 3rd year after treatment and before treatment [690 mg (160-5171) versus 120 mg (16-678) versus 400 mg (80-3200) versus 506 mg (40-2656), respectively; p=0.187].

DISCUSSION

In our study, the monthly total cost per patient was higher in the 16th week, 1st year, and 3rd year post-treatment compared to the pre-treatment period. The increase in the total post-treatment cost was largely caused by the increase in the direct medical cost. The

direct medical cost, in turn, increased largely due to the cost of omalizumab itself. The monthly emergency visit cost per patient as well as the monthly hospitalization cost per patient in the 16th week, 1st year, and 3rd year post-treatment was lower compared to the pre-treatment period. This study is the first to investigate this subject in Turkey. A serious drop was observed in the monthly number of attacks, emergency visits, hospitalizations, and patients using systemic steroids following treatment with Omalizumab. An increase was observed in ACT, FEV_1, and PEF values.

If we review other studies available in the literature, in a Polish study, Jahnz-Różyk et al. (19) found that the hospitalization cost per patient, the cost of emergency room visit, the number of office visits, and the dose of oral corticosteroids had decreased, while the total treatment cost increased. The researchers highlighted that this increase was largely due to the cost of omalizumab. In a Japanese study, omalizumab was not found to be cost-effective for patients with severe asthma and the authors suggested that cost-effectiveness could be achieved by lowering the price of omalizumab(20). Similarly, in an American study, omalizumab was not found to be cost-effective in patients with allergic asthma patients, whereby this was attributed to the high price of omalizumab (21). In a Canadian study, similarly to the above studies, Tadrous et al. (16) had found that omalizumab was not cost-effective in patients suffering from either moderate or severe asthma. Likewise, similar to the above-mentioned studies, the total cost after omalizumab treatment was found to be higher than the total cost before the treatment in our study. Conversely, we observed a dramatic decrease in the number of attacks, the number of emergency room visits, and the hospitalization costs during the post-treatment period. We believe that this may be associated with the high price of omalizumab, similar to what was observed in Japan and Poland, as well as associated with the low average emergency room visit fees and hospitalization costs in Turkey — the latter give that Turkey has lower average emergency and hospitalization costs compared to both the United States and much of Europe. Unlike our and the other aforementioned studies, it was shown in other studies from Ireland, Spain, Italy, Brazil, the Netherlands, and the United States that the omalizumab was both cost-effective and that led to a considerably lower number of hospitalizations, the number of emergency room visits, loss of productivity at work, oral corticosteroid use, and the number of outpatient clinic visits. Also, a marked increase was observed in FEV_1 and PEF values and quality of life (17,22-27).

When the data of the patients in our study, whose asthma control was unexpectedly deteriorated in the 3rd year and who had an increase in the number of attacks, emergency admissions, and therefore the hospitalization cost, were re-examined, it was observed that systemic steroid use was discontinued at the end of the 1st year in most of these asthmatic patients who were well controlled with omalizumab treatment. As a result, worsening of asthma may have been observed in the later periods of the patients. Our study consists of the analysis of real-life data, and the outcome of the patients was like this.

In a handful of other studies, it was emphasized that the omalizumab treatment had to be administered to select groups of patients suffering from severe asthma for it to be cost-effective as well as effective for clinical recovery (28,29).

The most significant limitation of our study is its retrospective design. The study was performed using the information available in patients' files. For this reason, this descriptive study provides an estimation of costs and outcomes for a defined patient group. Provided that our data did not allow for the calculating of the quality-adjusted life-year (QALY) and the incremental cost-effectiveness ratio (ICER), this study is related to the direct cost of omalizumab rather than the analysis of its cost-effectiveness. Nevertheless, we can say that it is clinically effective given that leads to a lower number of attacks, emergency room visits, and hospitalization rates. The lack of 3rd year follow-up data for some patients is also another limitation of our study. One of the important limitations of our study is that indirect cost (payments for missed workdays covered by the employee's disability and sick-leave program), could not be calculated.

CONCLUSION

We found that the addition of omalizumab to the treatment regime of patients diagnosed with severe allergic asthma led to a serious increase in the total post-treatment cost. Yet, we also observed a decrease in the average emergency room visit and hospitalization costs after the omalizumab treatment. We believe that reducing omalizumab prices in our country would provide a direct cost reduction in severe allergic asthma patients. Furthermore, prospective studies involving a greater number of patients are needed to better examine the direct cost analysis of omalizumab in the Turkish context.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Ankara Keçiören Training and Researchs Hospital Clinical Research Ethics Committee (Date: 12.27. 2017, Decision:1553).

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. Beasley R, of Asthma TIS. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The Lancet 1998; 351: 1225-32.
2. Şekerel BE, Türktaş H, Bavbek S, Öksüz E, Malhan S. Economic burden of pediatric asthma in Turkey: A Cost of Illness Study from payer perspective. Turk Thorac J 2020; 21: 248.
3. D'Amato G, Vitale C, Molino A, et al. Asthma-related deaths. Multidiscip Respir Med 2016; 11: 37.
4. Pakhale S, Mulpuru S, Boyd M. Optimal management of severe/refractory asthma. Clin Med Insights Circ Respir Pulm Med 2011; 5: 37-47.
5. Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. Thorax 2000; 55: 566-73.
6. Bavbek S, Malhan S, Mungan D, et al. Economic burden of severe asthma in Turkey: a cost of illness study from payer perspective. Eur Ann Allergy Clin Immunol 2021; 53: 128-37.
7. Çelik GE, Bavbek S, Paşaoğlu G, et al. Direct medical cost of asthma in Ankara, Turkey. Respiration 2004; 71: 587-93.
8. Bavbek S, Mungan D, Türktaş H, et al. A cost-of-illness study estimating the direct cost per asthma exacerbation in Turkey. Respir Med 2011; 105: 541-8.
9. Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. Am J Respir Crit Care Med 2001; 164: 6-11.
10. Lai T, Wang S, Xu Z, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. Sci Rep 2015; 5: 1-10.
11. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy 2005; 60: 302-8.
12. Chipps B, Buhl R, Beeh K-M, et al. Improvement in quality of life with omalizumab in patients with severe allergic asthma. Curr Med Res Opin 2006; 22: 2201-8.
13. Korn S, Thielen A, Seyfried S, et al. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. Respir Med 2009; 103: 1725-31.
14. Bavbek S, Aydın O, Kepil SÖ, et al. Therapy with omalizumab in patients with severe persistent allergic asthma: a real life data in Turkey. Tuberk Toraks 2010; 58: 425-34.
15. Yorgancıoğlu A, Öner Erkekol F, Mungan D, et al. Long-Term omalizumab treatment: a multicenter, real-life, 5-year trial. Int Arch Allergy Immunol 2018; 176: 225-33.
16. Tadrous M, Khuu W, Lebovic G, et al. Real-world health care utilization and effectiveness of omalizumab for the treatment of severe asthma. Ann Allergy Asthma Immunol 2018; 120: 59-65.
17. Suzuki C, Lopes da Silva N, Kumar P, Pathak P, Ong SH. Cost-effectiveness of omalizumab add-on to standard-of-care therapy in patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting. J Med Econ 2017; 20: 832-9.
18. Hochhaus G, Brookman L, Fox H, et al. Pharmacodynamics of omalizumab: implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. Curr Med Res Opin 2003; 19: 491-9.
19. Jahnz-Różyk K, Lis J, Warchoł M, Kucharczyk A. Clinical and economic impact of a one-year treatment with omalizumab in patients with severe allergic asthma within a drug programme in Poland. BMC Pulm Med 2018; 18: 48.
20. Morishima T, Ikai H, Imanaka Y. Cost-effectiveness analysis of omalizumab for the treatment of severe asthma in Japan and the value of responder prediction methods based on a multinational trial. Value Health Reg Issues 2013; 2: 29-36.
21. Wu AC, Paltiel AD, Kuntz KM, Weiss ST, Fuhlbrigge AL. Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. J Allergy Clin Immunol 2007; 120: 1146-52.
22. Costello R, Long D, Gaine S, et al. Therapy with omalizumab for patients with severe allergic asthma improves asthma control and reduces overall healthcare costs. Irish J Med Sci 2011; 180: 637-41.
23. Dal Negro RW, Tognella S, Pradelli L. A 36-month study on the cost/utility of add-on omalizumab in persistent difficult-to-treat atopic asthma in Italy. J Asthma 2012; 49: 843-8.
24. van Nooten F, Stern S, Braunstahl G-J, et al. Cost-effectiveness of omalizumab for uncontrolled allergic asthma in the Netherlands. J Med Econ 2013; 16: 342-8.
25. Levy AN, García a Ruiz AJ, García-Agua Soler N, Sanjuan MVH. Cost-effectiveness of omalizumab in severe persistent asthma in Spain: a real-life perspective. J Asthma 2015; 52: 205-10.
26. del Carmen Vennera M, Valero A, Uría E, Forné C, Picado C. Cost-effectiveness analysis of omalizumab for the treatment of severe persistent asthma in real clinical practice in Spain. Clin Drug Investig 2016; 36: 567-78.
27. Campbell J, Spackman D, Sullivan S. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. Allergy 2010; 65: 1141-8.
28. Faria R, McKenna C, Palmer S. Optimizing the position and use of omalizumab for severe persistent allergic asthma using cost-effectiveness analysis. Value Health 2014; 17 : 772-82.
29. Oba Y, Salzman GA. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. J Allergy Clin Immunol 2004; 114: 265-9.

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The evaluation of sepsis in the emergency department and its association with mortality

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ABSTRACT

Aim: Sepsis is a life-threatening organ dysfunction accompanied by a dysregulated host response to infection. Patients with sepsis may present with different clinical manifestations, and there is no gold standard diagnostic test. Early diagnosis and rapid treatment result in a decrease in sepsis-related deaths. Quick Sequential Organ Failure Assessment (qSOFA) is a scoring system used in diagnosing sepsis through a rapid evaluation at the time of initial presentation. The purpose of this study was to evaluate the relationship between qSOFA scores and mortality in patients presenting to the emergency department with suspected sepsis.

Material and Method: Seventy patients presenting to the Atatürk University Medical Faculty Emergency Department and commencing treatment with a preliminary diagnosis of sepsis between 01.12.2019 and 01.06.2020 were included in the research. Patients' qSOFA scores were calculated, and their demographic data, infection parameters and foci, the clinics to which they were admitted, and outcomes were recorded. The data were analyzed, and the relationships between qSOFA classifications and other infection parameters (CRP, procalcitonin, and lactate) and mortality were examined.

Results: Seventy percent (n=49) of the 70 patients in the study were discharged, while 30% (n=21) were exitus. A statistically significant relationship was present between qSOFA scores and mortality ($p<0.001$). CRP was also significantly related to qSOFA ($p=0.003$). Significant relationships were determined between CRP, procalcitonin and lactate and mortality ($p=0.009$, $p<0.001$, and $p=0.009$, respectively).

Conclusion: The use of qSOFA scores at initial assessment in the emergency department appears to be a simple and rapid means of diagnosing sepsis. qSOFA levels were significantly associated with mortality. CRP, procalcitonin, and lactate levels were also associated with mortality, and CRP was significantly associated with qSOFA. Early diagnosis and treatment can be expected to reduce mortality.

Keywords: Sepsis, qSOFA, Emergency, Mortality

INTRODUCTION

Millions of individuals are diagnosed with sepsis every year. One in four cases followed-up with a diagnosis of sepsis conclude with mortality. Rapid diagnosis of sepsis and the initiation of appropriate treatment affect the disease prognosis (1). New recommendations emerged from the Third International Consensus Definitions for Sepsis and Septic Shock in 2016. Sepsis was defined as a life-threatening organ dysfunction accompanied by a dysregulated host response to infection (2). It represents the body's response to an infection. The resulting exposure leads to the release of proinflammatory and anti-inflammatory mediators. These mediators can lead to organ failure and death in sepsis by affecting endothelial damage, vascular permeability, microvascular dysfunction, and coagulopathies (2, 3). Clinical findings in sepsis are variables associated with the source of the infection. The most widespread infection sites leading to sepsis are the respiratory, gastrointestinal, and genitourinary systems, the skin, and soft tissue. In addition to general clinical symptoms such as fever, hypotension, tachypnea, tachycardia, confusion, anxiety, respiratory difficulty, vomiting, decreased urine output, and hypoperfusion, it can also exhibit findings localized to the region of infection (4,5).

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The level of organ dysfunction occurring in sepsis is evaluated using various scoring systems based on clinical findings, laboratory data, or therapeutic interventions. Sequential Organ Failure Assessment (SOFA) is more frequently used under intensive care conditions, and requires partial arterial oxygen pressure (PaO2), platelet count, and creatinine and bilirubin levels for calculation. Quick SOFA (qSOFA) is a scoring system used in diagnosing sepsis through a rapid assessment at the time of initial presentation. The Third International Consensus Definitions for Sepsis and Septic Shock agreed that qSOFA scores could be helpful to clinicians since they could be applied at the bedside in patients outside the intensive care unit and does not involve laboratory data.

A respiratory rate ≥22 /min, systolic blood pressure ≤100 mmHg, and altered mental state are evaluated, each being scored between 0 and 3 (2). There is no gold standard diagnostic test. However, early diagnosis and rapid treatment result in a decrease in sepsis-related deaths. qSOFA is used as a predictive tool calculating the risk of mortality, rather than diagnosis, at the time of first presentation. The purpose of the present study was to investigate the relationship between qSOFA and mortality and other infection parameters (CRP, procalcitonin, and lactate).

MATERIAL AND METHOD

The study was performed following receipt of approval from the Atatürk University Medical Faculty Clinical Researchs Ethics Committee (Date: 26.12.2019, Decision No: B.30.2.ATA.0.01.00/54). Seventy patients aged over 18 presenting to the Atatürk University Medical Faculty Emergency Department and commencing treatment with a preliminary diagnosis of sepsis (Based on anamnesis, state of consciousness, vital signs, laboratory parameters, and clinical status) between 01.12.2019 and 01.06.2020 were included in the research. Age, gender, accompanying diseases, vital findings on arrival, and lactate levels, procalcitonin, and lactate levels were recorded. Altered consciousness, infection foci, and the clinical to which the patient was admitted were also noted. qSOFA scores were calculated on the basis of respiration rate ≥22/ min, altered mental state (a Glasgow Coma Scale score of 13 or less), and systolic blood pressure ≤100 mmHg. Patients were followed-up after admission in the clinic in terms of prognosis and mortality. The relationship between patients' qSOFA classifications and other infection parameters (CRP, procalcitonin, and lactate) and mortality was then examined.

Statistical Analysis

Descriptive methods were employed for demographic data. Normality of data distribution was evaluated using the Kolmogorov-Smirnov test. Data were analyzed on SPSS 23.0.0.1 software (SPSS, IBM, Armonk, NY, USA). The chi-square test and Fisher's Exact test were used in two-group comparisons. Non-parametric continuous data were compared between the groups using the Mann-Whitney U test. p values <0.05 were considered statistically significant.

RESULTS

Women constituted 28.6% (n=20) of the 70 patients in the study . The mean age of the patients was 71.61 years (±12.1 SD) (min 19, max 92). Patients' other laboratory and clinical data are shown in **Table 1**. No correlation with mortality was observed in terms of either gender (r<0.001 p=1.0) or age groups (r=3.630 p=0.057). No significant correlation was also observed between either gender (r=0.488 p=0.784) or age groups (r=0.363 p=0.834) and qSOFA scores. No exitus occurred among the patients with qSOFA scores of 1 in this research (n=9). However, exitus occurred in 13.5% (n=5) of the patients with scores of 2 and in 66.7% (n=16) of those with qSOFA scores of 3 (**Table 2**). Patients' qSOFA scores were significantly correlated with mortality (r=24.011 p<0.001) (**Table 2**).

Table 1. Patients' laboratory and clinical data

Clinical data		
qSOFA	**n**	**%**
1	9	12.9
2	37	52.9
3	24	34.3
Infection focus	**n**	**%**
Pulmonary infection	35	50.0
Urinary infection	22	31.4
Other	13	18.6
Clinic to which admitted	**n**	**%**
Intensive care	48	68.6
Ward	22	31.4
Mortality	**n**	**%**
Discharged	49	70.0
Exitus	21	30.0
Laboratory data		
CRP	**n**	**%**
5-100	18	25.7
100 or above	52	74.3
Total	70	100
Procalcitonin (ng/mL)		
0-5	53	75.7
5 or above	17	24.3
Total	70	100.0
Lactate (mmol/L)		
1-1.5	18	25.7
1.5 or above	52	74.3
Total	70	100.0

The most common infections were pulmonary infections at 50% (n=35), followed by urinary infections at 31.4% (n=22), and other infections at 18.6% (n=13) (**Table 1**). Analysis showed that 68.6% (n=48) of patients were admitted to the intensive care unit from the emergency department, while 31.4% (n=22) were transferred to the wards (**Table 1**). Exitus occurred in 41.7% (n=20) of the patients admitted to the intensive care unit compared to 4.5% (n=1) of those admitted to the wards (**Table 2**). Mortality rates differed significantly between the clinics (r=9.899 p=0.002) (**Table 1**).

qSOFA scores of 3 were determined in only 11.1% (n=2) of the patients with CRP values of 5-100, but in 42.3% (n=22) of those with CRP values exceeding 100. qSOFA scores were significantly correlated with CRP groups (r=11.731 p=0.003) (**Table 1**). No significant association was observed between qSOFA scores and procalcitonin (r=3.708 p=0.157) or lactate (r=4.159 p=0.125) groups (**Table 3**). Exitus occurred in 5.6% (n=1) of the patients with CRP values of 5-100, and in 38.5% (n=20) of those with CRP values exceeding 100. Significant correlation was observed between the CRP groups and mortality (r=6.895 p=0.009) (**Table 4**). Mortality was also significantly correlated with procalcitonin (r=23.089 p<0.001) and lactate (r=6.895 p=0.009) (**Table 4**).

DISCUSSION

Early identification and rapid appropriate treatment of sepsis, which is linked to high morbidity and mortality, will yield good results. The present study examined the relationship between qSOFA and mortality. Men constituted 71.4% of the patients taking part. Men have also constituted more than 50% of the patients with sepsis in previous studies (6-7). This distribution has been linked to lower urinary infection rates in women due to better compliance with hygiene rules, occupation exposure in men, and the prevalence of pulmonary infections deriving from smoking (8). The mean age of the patients in research into sepsis is generally greater than 60. Lifetime accumulation of cellular damage and increased comorbid diseases also increase the tendency to sepsis in patients (9-10). The mean age of the patients with sepsis in the present study was 71.6± 12.1 years.

The most common focus of infection in this study, at 50%, was the respiratory system, followed by urinary tract infection at 31.4%. Chen et al. detected pneumonia in 55.8% of patients, and urinary tract infection in 20.9% (10). Our findings are compatible with the previous literature.

In the present study, 68.6% of patients were admitted to the intensive care unit, while 31.4% were followed up on the wards. Mortality rates were 41.7% in the intensive

Table 2. Relationships between patients' qSOFA classes, infection foci, and clinics to which they were admitted, and mortality

Q Sofa	**Mortality**	**n=70**	**%**	
1	Discharged	9	100	
2	Discharged	32	86.5	r=24.011
	Exitus	5	13.5	
3	Discharged	8	33.3	p<0.001
	Exitus	16	66.7	
Infection focus	**Mortality**	**n=70**	**%**	
Pulmonary infection	Discharged	20	57.1	
	Exitus	15	42.9	
Urinary infection	Discharged	19	86.4	r=5.857
	Exitus	3	13.6	p=0.053
Other infection sites	Discharged	10	76.9	
	Exitus	3	23.1	
Clinic to which admitted	**Mortality**	**n=70**	**%**	
Intensive care	Discharged	28	58.3	r=9.899
	Exitus	20	41.7	
Ward	Discharged	21	95.5	p=0.002
	Exitus	1	4.5	

Table 3. Correlations between patients' CRP. procalcitonin. and lactate groups and qSOFA classes

CRP	**Q Sofa**	**n=70**	**%**	
5-100	1	6	33.3	
	2	10	55.6	r=11.731
	3	2	11.1	
100 and above	1	3	5.8	p=0.003
	2	27	51.9	
	3	22	42.3	
Procalcitonin (ng/mL)	**Q Sofa**	**n=70**	**%**	
0-5	1	8	15.1	
	2	30	56.6	
	3	15	28.3	r=3.708
5 and above	1	1	5.9	p=0.157
	2	7	41.2	
	3	9	52.9	
Lactate (mmol/L)	**Q Sofa**	**n=70**	**%**	
1-1.5	1	4	22.2	
	2	11	61.1	
	3	3	16.7	r=4.159
1.5 and above	1	5	9.6	p=0.125
	2	26	50.0	
	3	21	40.4	

Table 4. Correlations between patients' CRP, procalcitonin, and lactate groups and mortality

CRP	**Mortality**	**n=70**	**%**	
5-100	Discharged	17	94.4	
	Exitus	1	5.6	r=6.895
100 and above	Discharged	32	61.5	p=0.009
	Exitus	20	38.5	
Procalcitonin (ng/mL)	**Mortality**	**n=70**	**%**	
0-5	Discharged	45	84.9	
	Exitus	8	15.1	r=23.089
5 and above	Discharged	4	23.5	p<0.001
	Exitus	13	76.5	
Lactate (mmol/L)	**Mortality**	**n**	**%**	
1-1.5	Discharged	17	94.4	
	Exitus	1	5.6	r=6.895
1.5 and above	Discharged	32	61.5	p=0.009
	Exitus	20	38.5	

care unit and 4.5% on the wards. It was seen that the use of clinical, radiological and laboratory results together with the qSOFA score in the patient evaluation in the emergency department provided more accurate referrals and treatment in appropriate clinics. Seymour et al. reported a mortality rate of 4-11% for non-intensive care patients, compared to 18% for those in intensive care (11). The total mortality rate among the patients with sepsis in the present study was 30%, while A charya et al. reported a rate of 40% in patients with sepsis (12), and Khwannimit et al. a rate of 45% among all patients (13).

The qSOFA score that emerged from the Third International Consensus Definitions for Sepsis and Septic Shock published in 2016 entered into use after being recommended as a good prognostic factor in predicting mortality in non-intensive care patients and admission to the intensive care unit (2). Examination of the association between qSOFA and mortality in the present study revealed no mortality in qSOFA group 1, a rate of 13.5% in qSOFA group 2, and a rate of 66.7% in qSOFA group 3. Wang et al. investigated 477 emergency department patients diagnosed with infection and reported no difference in 28-day mortality and ICU admission rates between groups with qSOFA scores of 0 and 1. However, an increase was reported in case of qSOFA scores higher than 1. Mortality in patients with qSOFA ≥2 was 2.5 times higher than in those with qSOFA <2, while the rate of admission to intensive care was 2.1 times higher (13). Another study reported qSOFA ≥2 in 24% of patients with infection, with a mortality rate of 70% in that group. A 3-14-fold increase in in-hospital mortality rates was observed in patients with qSOFA ≥2 (10). Freund Y. et al. reported that qSOFA exhibited 70% sensitivity and 79% specificity. Mortality occurred in only 3% of patients with qSOFA <2 (15). The findings of the present study are compatible with the previous literature, and mortality increased in patients with qSOFA ≥2.

Studies have emphasized lactate as an important parameter in the diagnosis and follow-up of sepsis (16). Lactate is continuously manufactured by red blood cells and certain tissue with high glycolysis rates, even at times when tissue perfusion is not impaired. The liver converts the majority of this lactate back to glucose and oxidizes the remainder. Sepsis-related hepatic dysfunction can therefore impair lactate clearance (17, 18).

Lactate was not used in the definition of sepsis in the Third International Consensus. It was only recommended in the definition of septic shock (2). One multi-center retrospective study no significant change in mortality or intensive care outcomes in patients with suspected sepsis at the time of admission, when qSOFA scores at presentation were reassessed with the addition of lactate ≥2 mmol/L to admission (11). Caseserly et al. reported that a combination of lactate ≥4mmol/L and hypotension was a good predictor of prognosis. Those authors also reported that low presentation lactate levels were of low prognostic value, but that serial lactate measurements and treatment being adjusted accordingly reduced mortality rates in patients admitted to intensive care (19). Similarly, in the present study, mortality occurred in only 5.6% (n=1) of patients with lactate levels of 1-1.5 mmol/L, but in 38.5% (n=20) of those with levels of 1.5 mmol/L or above. This difference between the lactate groups in terms of mortality was statistically significant. However, no significant correlation was determined between qSOFA scores and lactate groups. The majority of research has investigated serial lactate measurement rather than lactate values at time of presentation, while post-treatment lactate values have been considered, and interpretations have been produced by combining these with other clinical data (20).

Rather than being used as a diagnostic tool, the international sepsis guideline recommended procalcitonin (PCT) as capable of use in shortening the antibiotic period, and in narrowing and discontinuing treatment (19) Zhenyu et al.'s study of 102 cases of sepsis found that PCT was correlated with mortality (21). Castelli et al. reported that PCT predicted the severity and prognosis of sepsis, and that PCT concentrations were directly related to the criticality of sepsis and positively correlated with SOFA scores (22). In the present study, mortality occurred in 15.1% (n=8) of patients with PCT levels of 0-5 ng/mL, but in 76.5% (n=13) of those with PCT values of 5 ng/mL or above. The difference in mortality rates between the PCT groups was statistically significant. However, no significant association was determined between qSOFA scores and the PCT groups. While PCT elevation can be used as a test supporting diagnosis in patients with suspected bacterial infection, it does not discriminate between complicated and uncomplicated infections. It is not therefore sufficient by itself for use in diagnosis sepsis in the emergency department.

CRP is a well-known biomarker of infection and inflammation. Synthesis of this acute phase reactant is controlled by the liver. Although its principal disadvantage as a biomarker of sepsis in adults is low specificity, it is widely employed for screening early onset sepsis (occurring in the first 24 h), since its sensitivity is generally regarded as very high in that context (23). Saeed et al. determined a mean CRP level of 102 mg/dL in an exitus group, compared to 30 mg/dL in the surviving group (24). Yamamoto et al. suggested that mortality rates were four times higher in patients with CRP values higher than 150 mg/dL compared to those with values of 0-19.9 mg/dl (25). In the present study, mortality occurred in only 5.6% (n=1) of the patients with

CRP values of 5-100, but in 38.5% (n=20) in those with values above 100. Significant differences were observed between the CRP groups in terms of qSOFA and. CRP elevation is a supportive parameter in the early diagnosis and follow-up of sepsis due to its significant relationship with qSOFA and mortality.

CONCLUSION

qSOFA is correlated with mortality, and is a simple, rapid, inexpensive, and valid method of determining sepsis risk rates in patients with suspected infection outside the intensive care unit. However, more reliable and rapid tests than qSOFA are needed in the diagnosis of sepsis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was performed following receipt of approval from the Atatürk University Medical Faculty Clinical Researchs Ethics Committee (Date: 26.12.2019, Decision No: B.30.2.ATA.0.01.00/54).

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. Liu V, Escobar GJ, Greene JD, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA 2014; 312: 90-2.
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801-10.
3. Perman SM, Goyal M, Gaieski DF. Initial emergency department diagnosis and management of adult patients with severe sepsis and septic shock. Scand J Trauma Resusc Emerg Med 2012; 20: 41.
4. Gauer RL. Early recognition and management of sepsis in adults: the first six hours. Am Fam Physician 2013; 88: 44-53.
5. Esper AM, Moss M, Lewis CA, Nisbet R, Mannino DM, Martin GS. The role of infection and comorbidity: Factors that influence disparities in sepsis. Crit Care Med 2006; 34: 2576-82.
6. Cheng B, Li Z, Wang J, et al. Comparison of the Performance Between Sepsis-1 and Sepsis-3 in ICUs in China: A Retrospective Multicenter Study. Shock 2017; 48: 301-6.
7. Raith EP, Udy AA, Bailey M, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA 2017; 317: 290-300.
8. Rhee C, Jones TM, Hamad Y, et al. Prevalence, underlying causes, and preventability of sepsis-associated mortality in US Acute Care Hospitals. JAMA Netw Open 2019; 2: e187571.
9. Milbrandt EB, Eldadah B, Nayfield S, Hadley E, Angus DC. Toward an integrated research agenda for critical illness in aging. Am J Respir Crit Care Med 2010; 182: 995-03.
10. Chen QH, Shao J, Liu WL, et al. Predictive accuracy of Sepsis-3 definitions for mortality among adult critically ill patients with suspected infection. Chin Med J (Engl) 2019; 132: 1147-53.
11. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 762-74.
12. Acharya SP, Pradhan B, Marhatta MN. Application of "the Sequential Organ Failure Assessment (SOFA) score" in predicting outcome in ICU patients with SIRS. Kathmandu Univ Med J (KUMJ) 2007; 5: 475-83.
13. Khwannimit B, Bhurayanontachai R, Vattanavanit V. Comparison of the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure among sepsis patients admitted to the intensive care unit in a middle-income country. J Crit Care 2018; 44: 156-60.
14. Wang JY, Chen YX, Guo SB, Mei X, Yang P. Predictive performance of quick Sepsis-related Organ Failure Assessment for mortality and ICU admission in patients with infection at the ED. Am J Emerg Med 2016; 34: 1788-93.
15. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic accuracy of Sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. JAMA 2017; 317: 301-08.
16. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 775-87.
17. Toffaletti JG. Blood lactate: biochemistry, laboratory methods, and clinical interpretation. Crit Rev Clin Lab Sci 1991; 28: 253-68.
18. Garrabou G, Morén C, López S, et al. The effects of sepsis on mitochondria. J Infect Dis 2012; 205: 392-400.
19. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017; 43: 304-77.
20. Chertoff J, Chisum M, Simmons L, King B, Walker M, Lascano J. Prognostic utility of plasma lactate measured between 24 and 48 h after initiation of early goal-directed therapy in the management of sepsis, severe sepsis, and septic shock. J Intensive Care 2016; 4: 13.
21. Li Z, Wang H, Liu J, Chen B, Li G. Serum soluble triggering receptor expressed on myeloid cells-1 and procalcitonin can reflect sepsis severity and predict prognosis: a prospective cohort study. Mediators Inflamm 2014; 2014: 641039.
22. Castelli GP, Pognani C, Cita M, Stuani A, Sgarbi L, Paladini R. Procalcitonin, C-reactive protein, white blood cells and SOFA score in ICU: diagnosis and monitoring of sepsis. Minerva Anestesiol 2006; 72: 69-80.
23. Hofer N, Zacharias E, Müller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology 2012; 102: 25-36.
24. Saeed K, Wilson DC, Bloos F, et al. The early identification of disease progression in patients with suspected infection presenting to the emergency department: a multi-centre derivation and validation study. Crit Care 2019; 23: 40.
25. Yamamoto S, Yamazaki S, Shimizu T, et al. Prognostic utility of serum CRP levels in combination with CURB-65 in patients with clinically suspected sepsis: a decision curve analysis BMJ Open 2015; 5: e007049.

Original Article

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Investigation of the relationship between placenta trace element levels and methylated arginines

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ABSTRACT

Aim: Environmental exposure and maternal nutrition are vital for placental and fetal development during pregnancy. Essential elements such as zinc, copper and selenium are important elements that are needed for human growth and development. Research indicates that methylated arginines play a key role in pregnancy and offspring outcomes. The aim of the study was to compare the placental tissue levels of trace elements and methylated arginines. In addition, we aimed to evaluate this placental trace elements and methylated arginine levels in terms of placental and birth weight.

Material and Method: This is a case-control study with 133 pregnant women. Two groups were formed: women with higher risk of exposure to chemicals (working in chemistry, metal and other industrial sectors) and those with no risk of exposure to hazardous chemicals (house wives and working in other non-hazardous workplaces). Placenta zinc, copper and selenium and asymmetric dimethylarginine, symmetric dimethylarginine, arginine, citrulline, homoarginine and L-N-monomethyl arginine levels were investigated.

Results: There was a positive correlation between birth weight with copper, L-N-monomethyl arginine, total methylarginines; there was a negative relationship between birth weight and asymmetric dimethylarginine, symmetric dimethylarginine, arginine, citrulline. However, no statistically significant relationship was found between trace elements such as zinc, copper and selenium with methylated arginines, except for L-N-monomethyl arginine ($r=0.178$; $p<0.05$).

Conclusion: Zinc, copper and selenium levels are not related to processes that reduce birth weight and vascular factors.

Keywords: Essential elements, methylated arginines, placental weight, birth weight, placenta tissue

INTRODUCTION

Essential elements such as zinc (Zn), copper (Cu) and selenium (Se) are important elements for human growth and development (1,2). Zn is involved in metabolic and physiological processes that control cell growth, while Cu plays an important role in the absorption and metabolism of Fe. On the other hand, Se is the most well-known trace element necessary for metabolism of organism (2,3). Low levels of Zn and Cu are independently associated with a risk of low birth weight (4,5).

Environmental exposures and maternal nutrition are vital for placental and fetal development during pregnancy (4,6–8). Arginine, a semi-essential amino acid, is a precursor in the synthesis of many molecules including nitric oxide and polyamines (8,9). Arginine plays a decisive role in nutrition and metabolism, acting as a precursor for the synthesis of biologically important substances (6,7). Nitric oxide (NO) and polyamines play a decisive role during pregnancy and fetal development (8). Furthermore, these molecules are key regulators of angiogenesis (10). Several studies have demonstrated that polyamines and NO are essential for placental growth and angiogenesis, therefore increasing uterine and placental–fetal blood flow (11).

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Asymmetric dimethyl arginine (ADMA) is a competitive endogenous inhibitor of nitric oxide (NO) synthase which plays a role in the regulation of NO synthesis (12). Maternal plasma ADMA levels decrease in early stage of gestation but increase as the gestational age increases (13). Asymmetric dimethyl arginine is generated when arginine residues in the nuclear proteins are methylated through the action of the protein arginine methyltransferases (12,14,15). Types of protein arginine methyltransferases were type 1, catalyzing the formation of ADMA, and type 2, catalyzing the formation of the symmetric dimethyl arginine (SDMA); both generating the NG-monomethyl-L-arginine (L-NMMA). While asymmetrical methylated species (ADMA and L-NMMA) can inhibit NOS, SDMA cannot (16,17). The vascular endothelium lined with endothelial cells plays a critical role in the mechanics of blood flow, and ADMA antagonizes endothelium-dependent vasodilation. ADMA is accepted to be a strong and independent risk factor of total mortality and inverse vascular outcomes (12,18,19). Citrulline has limited degradation in the placenta, is efficiently transferred from maternal circulation to fetus in favor of fetal development (20). Research indicates that methylated arginines play a key role in pregnancy and offspring outcomes.

The aim of this study is to compare the placental tissue levels of trace elements such as Zn, Cu, and Se and methylated arginines such as ADMA, SDMA, arginine, citrulline, homoarginine and L-NMMA. In addition, we aimed to evaluate the relationship between levels of placental trace elements and methylated arginine levels and placental weight and birth weight.

MATERIAL AND METHOD

This study was conducted with the approval of Lokman Hekim University Ethics Committee (Date: 24.12.2020, Decision No:2020/008-008). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Area and Design

This study was conducted at the Department of Obstetrics and Gynecology, Liv Hospital, Ankara, Turkey. In the case of a positive pregnancy test, the women were asked to donate placental tissue sample for future analysis and thereafter were invited to the hospital for further examination. 133 women were enrolled in the study. Oral and written informed consent was granted by all women involved in the study. The placenta tissue samples for all analyses including essential elements and methylated arginines collected and stored -20°C until pre-analyses. These samples are collected for analyses of Zn, Cu, Se, ADMA, SDMA, arginine, citrulline, homoarginine and L-NMMA levels. We included women with a singleton pregnancy between 34 and 41 weeks of gestation. The control group included gestational age-matched pregnant women who had clinically healthy pregnancies without any complications. We formed two groups in the occupational exposure risk of mother: Group 0 with the low-risk maternal occupation and Group 1with high-risk maternal occupation). Information related to age, body mass index (BMI), socioeconomic status (SES), parity, gestational days, characteristics of the new-born (birth weight, birth length and head circumference) and placental weight were evaluated within the scope of the study. Two groups were formed: women with higher risk of exposure to chemicals (working in chemistry, metal and other industrial sectors) and those with no risk of exposure to hazardous chemicals (house wives and working in other non-hazardous workplaces).

Laboratory Analysis of Zn, Cu, Se and Methylated Arginine Derivatives

Placenta tissues were stored frozen, after thawing at room temperature; the wet tissues were weighed on a precision scale, and then transferred onto a glass table. The surfaces of the glass tray and table were pre-dried at 75°C for 24 h in an incubator. Tissue samples collected from the incubator (approximately 0.2 gr per sample) were weighed to determine dry matter using a precision scale and transferred to high temperature resistant microwave Teflon tubes. Dry tissue weights were used in all calculations related to placenta. All tissue samples were digested by Microwave Digestion System (Start D, Milestone, USA). Briefly, 10 ml of nitric acid (Suprapur®, 65% HNO_3) was added to the tissues, acid etching was performed in the microwave and the tissue specimens were transferred to 15 ml polypropylene tubes (Isolab) with a rotary cap. The total volume was adjusted to 10 ml with ultrapure water (4). The placenta samples Zn, Cu and Se levels were determined using inductively coupled plasma mass spectrometry (ICP-MS, Thermo Scientific ICAPQc, USA). The operating parameters were set as follows: radiofrequency power 1550 W, nebulizer gas 0.97 L/min, plasma gas 0.9 L/min, nebulizer pressure 3.00 bar, dwell time 0.01 milliseconds, and spray chamber temperature 3.6°C. The sampler probe was washed between injections by rinsing with ultrapure water for 30 s, followed by washing with 2% HNO_3 for 45 s, and finally rinsing with ultrapure water for 45 s. After the washing steps, the instrument automatically ran the next sample. A 9-point (0.5–250 ppb) calibration curves were formed for Zn, Cu and Se. A minimum R value of 0.9985 was calculated for all calibrations. The limit of detection (LOD) of Zn, Cu and Se were determined based on the standard deviation of the response and the slope of the calibration curves (3). Method validations were performed with the certified material (Whole Blood L-2, Sero AS, Norway).

The placenta tissue ADMA, SDMA, arginine, citrulline, homoarginine and L-NMMA levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, according to the manufacturer's instructions. The reading of the samples placed on the microplates was done with an ELISA device (BMG LABTECH, UK) with a wavelength of 450 nm. Samples were thawed and each sample was placed on 96-well flat microplates supplemented with 50 µL incubation buffers. The microplate was then incubated for 45 min at 37°C. After washing and aspiration of microplates (3 times each), 100 µL of conjugate was added to the microplates, followed incubate for 30 min at 37°C. 90 µL of Reagent was added after second aspiration and washing (5 times each). This was followed for 15 min at 37°C. Subsequently, stop solutions on microplates were added. Control materials used for optimization and for validity of the ELISA methods. Control samples will be used for verification. The analysis was done in 5 points according to the calibration curves created against the standard measurements in the ELISA device. Each kit was read at least 10 times and regression analysis was performed by taking the averages.

Statistical Analysis

The SPSS 20.0 software was used in statistical analysis. The suitability of the parameters to the normal distribution was evaluated with the Kolmogorov Smirnov test. It was observed that the data were normally distributed and parametric tests were applied. Continuous variables were presented with their mean and standard deviations. The difference between the two means was evaluated with the t-test, and the relations of the variables with each other were evaluated with Pearson Correlation analysis. $p<0.05$ and $p<0.01$ values were considered significant.

RESULTS

According to Pearson correlation coefficients; there was a positive correlation between birth weight with Cu (r=0.237; p<0.01), L-NMMA (r=0.202; p<0.05), total methylarginines (r=0.177; p<0.05); there was a negative relationship between birth weight and ADMA (r= -0.413; p<0.01), SDMA (r= -0.273; p<0.01), arginine (r= -0.192; p<0.05), citrulline (r= -0.220; p<0.05). However, no statistically significant relationship was found between trace elements such as Zn, Cu and Se with methylated arginines (p>0.05), except for L-NMMA (r=0.178; p<0.05). The correlation between clinical parameters is presented in **Table 1**.

Maternal age, gestational days, birth length, hematocrit (HCT), Zn, Cu, Se, ADMA, SDMA, arginine, citrulline, homoarginine, L-NMMA, arginine / ADMA ratio, SDMA / ADMA and total methylarginine values were not statistically different between groups (p> 0.05).

Table 1. The correlation between clinical parameters

	Birth Weight	Age	Gestational days	HGB	HCT	Cu	Zn	Se	ADMA	SDMA	Arginine	Citrulline	Homoarginine	L-NMMA	Arginine/ ADMA ratio	SDMA/ADMA ratio
Age	-0.15	1														
Gestational days	0.083	.203*	1													
HGB	0.117	-0.05	-0.02	1												
HCT	0.094	-.191*	-0.1	.442**	1											
Cu	.237**	-0.15	-0.15	0.04	.186*	1										
Zn	-0.09	-0.12	-0.17	0.13	0.01	0.15	1									
Se	-0.08	-0.09	-.183*	0.089	0.024	0.106	.877**	1								
ADMA	-.413**	0.159	-0.13	-.254**	-0.08	-0.15	0.028	0.12	1							
SDMA	-.273**	0.118	-0.06	-0.15	0.011	0.009	0.017	0.096	.572**	1						
Arginine	-.192*	0.131	-0.03	-.193*	-0.05	-0.11	-0.07	0.002	.257**	.176*	1					
Citrulline	-.220*	0.106	-0.1	-0.07	-0.05	-0.01	-0.02	-0.01	.205*	0.154	.405**	1				
Homoarginine	0.004	0.043	-0.17	-0.02	-0.07	0.106	-0.11	-0.14	.216*	.186*	0.15	0.105	1			
L-NMMA	.202*	-0.04	-0.02	-0.02	-0.01	0.014	.178*	0.125	-.174*	-0.1	-.239**	-0.13	-.200*	1		
Arginine/ ADMA ratio	0.013	0.064	0.029	-0.07	-0.02	-0.05	-0.09	-0.05	-.194*	-0.07	.878**	.291**	0.074	-0.16	1	
SDMA/ADMA ratio	0.115	-0.08	0.075	0.103	0.097	0.152	0.024	0.008	-.395**	.502**	-0.05	-0.05	-0.01	0.062	0.152	1
Total methylarginines	.177*	0.079	-0.11	-0.15	0.05	0.083	0.034	0.14	.649**	.786**	0.128	0.087	.243**	0.091	-0.15	.188*

In spite of that, placental weight values for mothers with low-risk occupation group was found statistically significantly higher than mothers with occupations that have higher risk for chemical exposure (p<0.05). On the contrary, hemoglobin (HGB) levels were found to be statistically significantly lower in mothers with low risk of exposure (p<0.05). However, the difference was not clinically significant. Therewithal, birth weights were higher for the offspring of mothers with low risk of exposure, however the difference was not statistically significant (p>0.05). Main clinical parameters of variables according to maternal occupation groups presented in **Table 2**.

Table 2. The relationship between clinical parameters according to the occupational exposure risk of mother (0- low-risk maternal occupation group; 1-high-risk maternal occupation group).

	Groups	n	Mean	Std. Deviation	p
Maternal Age (years)	0	118	27.82	5.52	>0.05
	1	15	28.87	5.64	
Gestational Days	0	118	257.58	26.75	>0.05
	1	15	265.07	22.89	
Placental Weight (gr)	0	118	576.65	77.30	<0.05*
	1	15	533.00	76.90	
Birth Weight (gr)	0	118	3181.08	417.32	>0.05
	1	15	3057.33	515.08	
Birth Length (cm)	0	118	49.05	3.80	>0.05
	1	15	50.07	3.17	
Head Circumference	0	118	33.82	1.20	>0.05
	1	15	34.40	1.06	
HGB	0	118	12.05	1.50	<0.05*
	1	15	13.03	1.99	
HCT	0	118	38.13	14.20	>0.05
	1	15	39.39	14.13	
Cu [ug/g]	0	118	27.03	18.64	>0.05
	1	15	25.17	21.38	
Zn [ug/g]	0	118	77.77	110.21	>0.05
	1	15	96.82	160.62	
Se [ug/g]	0	118	2.92	3.09	>0.05
	1	15	3.25	4.20	
ADMA (umol/L)	0	118	0.73	0.16	>0.05
	1	15	0.71	0.14	
SDMA (umol/L)	0	118	0.91	0.22	>0.05
	1	15	0.90	0.12	
Arginine (umol/L)	0	118	669.97	305.90	>0.05
	1	15	663.35	288.43	
Citrulline (umol/L)	0	118	52.27	41.39	>0.05
	1	15	52.68	39.08	
Homoarginine (umol/L)	0	118	3.04	2.36	>0.05
	1	15	2.67	2.62	
L-NMMA (umol/L)	0	118	0.07	0.06	>0.05
	1	15	0.06	0.05	
Arginine/ ADMA oranı	0	118	937.90	457.63	>0.05
	1	15	927.94	350.15	
SDMA/ ADMA oranı	0	118	1.26	0.25	>0.05
	1	15	1.29	0.17	
Total methylarginines (umol/L)	0	118	1.93	0.33	>0.05
	1	15	1.83	0.27	

While a statistically significant negative correlation was found between birth weight and maternal age mothers with high risk of occupational exposure (r=-0.720; p<0.01), this relationship was not significant in the low-risk group (r=-0.530; p>0.05).

Essential element levels and birth weight were compared according to the occupational exposure risk with Pearson correlation coefficients. There was a positive correlation between Cu and birth weight values in low-risk maternal occupation group (r=0.340; p<0.01). On the other hand, there was no significant relationships birth weight with other trace elements. **Figure 1** shows relationships between birth weight and analyzed trace elements.

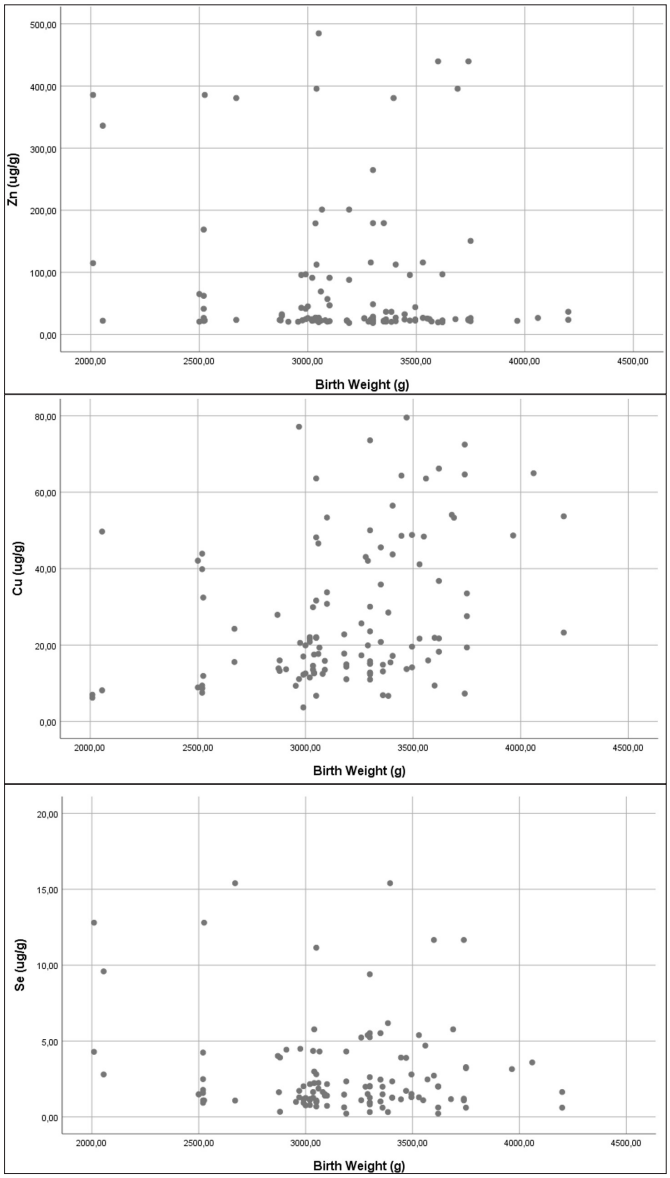

Figure 1. The relationship between birth weight and analyzed trace elements such as Zn, Cu and Se.

DISCUSSION

The main finding of this study was a negative relationship between birth weight and ADMA, SDMA, arginine and citrulline values. A recent study showed that maternal plasma ADMA concentration may be an indicator of fetal growth restriction (21).

Cu plays a role in both antioxidant and prooxidant events in human body (3). This element regulates the functions of several cuproenzymes that are essential for life (22). Copper is a trace element which is required for the functioning of variety cellular enzymes (23,24). The data about the relationship between trace elements especially Cu and methylated arginines is conflicting. Copper amine oxidase, which modulates NO production by regulating arginase activity, affects the bioavailability of arginine (25).

Strong immune response needs adequate level of micronutrients. Zn, Cu, vitamin A, vitamin D, vitamin C, vitamin E and other trace elements and vitamins, all of them are described as micronutrient (23). Oral arginine supplementation improved fetoplacental blood flow distribution in pregnant women with threatened preterm labor. These observations suggest that arginine supplementation might have a beneficial effect on preterm birth (8). On the other hand, a positive correlation was found between Cu levels and birth weight in this study. Özdemir et al. (22) suggested that copper may impair fetal growth with its negative effect on SOD1 enzyme. In the same study, they also stated that Zn did not have a negative effect on fetal growth. Although, copper was found to have a strong positive correlation with birth weight in the whole group in our study. In this context, while there was a significant relationship in the low-risk maternal occupational exposure group, no relationship was found in high-risk group. This suggests other factors came into play in the low-risk group. On the other hand, there was no significant relationship between birth weight and other trace elements such as Zn and Se. However, no statistically significant relationship was found between analyzed trace elements with methylated arginines, except for L-NMMA. The reason for the lack of this relationship is that low birth weight in trace element deficiency is not associated with vascular factors. Therefore, it would be appropriate to investigate the relationship of other toxic exposures with this situation in different groups.

CONCLUSIONS

In conclusion, according to the data we obtained in our study, Zn and Se trace elements are not related to processes that reduce birth weight and vascular factors. However, a strong positive correlation was found between Cu levels and birth weight in this study. This also suggest us to question the necessity of these supplements during pregnancy.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted with the approval of Lokman Hekim University Ethics Committee (Date: 24.12.2020, Decision No:2020/008-008).

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. Abass RM, Hamdan HZ, Elhassan EM, Hamdan SZ, Ali NI, Adam I. Zinc and copper levels in low birth weight deliveries in Medani Hospital, Sudan. BMC Res Notes 2014; 7: 386.
2. Kot K, Kosik-Bogacka D, Łanocha-Arendarczyk N, et al. Interactions between 14 Elements in the Human Placenta, Fetal Membrane and Umbilical Cord. Int J Environ Res Public Health 2019; 16: 1615.
3. Turan E, Turksoy VA. Selenium, Zinc, and Copper Status in Euthyroid Nodular Goiter: A Cross-Sectional Study. Int J Prev Med 2021; 12: 46.
4. Turksoy VA, Yalvac ES, Simsek OT, et al. Impact of zinc on birth and placental weight in cadmium and lead exposure during pregnancy. Indian J Forensic Med Pathol 2019; 12: 246–54.
5. Roels HA, Bowler RM, Kim Y, et al. Manganese exposure and cognitive deficits: a growing concern for manganese neurotoxicity. Neurotoxicology 2012; 33: 872-80.
6. Wu G, Morris SM Jr. Arginine metabolism: nitric oxide and beyond. Biochem J. 1998; 336: 1-17.
7. Wu G, Bazer FW, Satterfield MC, et al. Impacts of arginine nutrition on embryonic and fetal development in mammals. Amino Acids 2013; 45: 241-56.
8. Hsu CN, Tain YL. Impact of arginine nutrition and metabolism during pregnancy on offspring outcomes. Nutrients 2019; 11: 1–15.
9. Wu G, Bazer FW, Davis TA, et al. Arginine metabolism and nutrition in growth, health and disease. Amino Acids 2009; 37: 153-68.
10. Zhao X, Lu X, Feng Q. Deficiency in endothelial nitric oxide synthase impairs myocardial angiogenesis. Am J Physiol Heart Circ Physiol 2002; 283: H2371-H2378.
11. Gao K, Jiang Z, Lin Y, et al. Dietary L-arginine supplementation enhances placental growth and reproductive performance in sows. Amino Acids 2012; 42: 2207-14.
12. Tutkun L, Gunduzoz M, Turksoy VA, et al. Assessment of Endothelial Dysfunction with Methylated Arginines and L-arginine in Cadmium-Exposed People: a Pilot Study. Clin Lab 2019; 65: 10.7754/Clin.Lab.2019.181249.

13. Fickling SA, Williams D, Vallance P, Nussey SS, Whitley GS. Plasma concentrations of endogenous inhibitor of nitric oxide synthesis in normal pregnancy and pre-eclampsia. Lancet. 1993; 342: 242-3.

14. Emrich IE, Zawada AM, Martens-Lobenhoffer J, et al. Symmetric dimethylarginine (SDMA) outperforms asymmetric dimethylarginine (ADMA) and other methylarginines as predictor of renal and cardiovascular outcome in non-dialysis chronic kidney disease. Clin Res Cardiol 2018; 107: 201-13.

15. Martens-Lobenhoffer J, Bode-Böger SM. Amino acid N-acetylation: metabolic elimination of symmetric dimethylarginine as symmetric N(α)-acetyldimethylarginine, determined in human plasma and urine by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 2015; 975: 59-64.

16. Griffioen AW, Molema G. Angiogenesis: potentials for pharmacologic intervention in the treatment of cancer, cardiovascular diseases, and chronic inflammation. Pharmacol Rev 2000; 52: 237-268.

17. Wada K, Inoue K, Hagiwara M. Identification of methylated proteins by protein arginine N-methyltransferase 1, PRMT1, with a new expression cloning strategy. Biochim Biophys Acta 2002; 1591: 1-10.

18. Zoccali C, Bode-Böger S, Mallamaci F, et al. Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. Lancet 2001; 358: 2113-7.

19. Shao J, Hou L, Liu J, et al. Indoleamine 2,3-Dioxygenase 1 Inhibitor-Loaded Nanosheets Enhance CAR-T Cell Function in Esophageal Squamous Cell Carcinoma. Front Immunol 2021; 12: 661357.

20. Lassala A, Bazer FW, Cudd TA, et al. Intravenous administration of L-citrulline to pregnant ewes is more effective than L-arginine for increasing arginine availability in the fetus. J Nutr 2009; 139: 660-5.

21. Tsikas D, Bollenbach A, Savvidou MD. Inverse correlation between maternal plasma asymmetric dimethylarginine (ADMA) and birthweight percentile in women with impaired placental perfusion: circulating ADMA as an NO-independent indicator of fetal growth restriction?. Amino Acids 2018; 50: 341-51.

22. Ozdemir U, Gulturk S, Aker A, Guvenal T, Imir G, Erselcan T. Correlation between birth weight, leptin, zinc and copper levels in maternal and cord blood. J Physiol Biochem 2007; 63: 121-8.

23. The Potential Role of Arginine/Glutamine/Zinc/Copper as Supplemental Immuno-Enhancing Nutrients in Suspected/Infected Sars-Cov-2 Patients. Iar J Med Sci 2020; 1: 20-25.

24. Tapiero H, Townsend DM, Tew KD. Trace elements in human physiology and pathology. Copper. Biomed Pharmacother 2003; 57: 386-98.

25. Groß F, Rudolf EE, Thiele B, Durner J, Astier J. Copper amine oxidase 8 regulates arginine-dependent nitric oxide production in Arabidopsis thaliana. J Exp Bot 2017; 68: 2149-62.

Review

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Adolescent suicide: an overview

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ABSTRACT

Suicide is the second leading cause of death among 15-19 years old group globally. Recent years suicidal thoughts and attempts have increased in adolescents. While Turkey is among the countries with a low suicide rate, the last ten-year statistics show that suicide attempts have steadily increased especially among young people. The aim of this review is to determine the factors that cause suicide and to identify the necessary measures to prevent adolescent suicides.

Keywords: Adolescent, COVID-19, mental health, self-harm, suicide, prevention

INTRODUCTION

Suicide is the act of intentionally causing one's own death directly or indirectly by a positive or negative action. World Health Organisation (WHO) described the act of suicide as "self-harm with the awareness of one's purpose and with varying degrees of lethal purpose" in 1974 (1). The actions carried out with the intention of death but not resulting in death are defined as suicide attempt and the actions resulting in death are defined as completed suicide (2).

Suicidal thoughts and attempts have increased among adolescents in recent years (3). Moreover, suicide is the second leading cause of death among 15-19 years old group globally (4). While Turkey is one of the countries with a low suicide rate, the statistics show that suicide attempts have steadily increased especially among young people over the past 10 years (5). In the last 10 years, approximately 27,500 people in Turkey lost their life because of suicide and 34.3% of the people who attempted suicide were in 15-29-year-old group (6,7). As a serious public health problem in this review, we aimed to determine the factors that cause suicide, to reveal the features and to identify the necessary measures to prevent adolescent suicides.

Factors Affecting Suicidal Behavior

There are many personal, social and environmental risk factors and also there are protective factors for adolescent suicides. Personal risk factors include family history of suicide or suicide attempts; history of adoption, male gender; parental mental disorders, lesbian, gay, bisexual, or questioning sexual orientation (LGBTQ); transgender identification, a history of physical or sexual abuse; pathologic Internet use, mental disorders, nonsuicidal self-injury (NSSI), and a previous suicide attempt. Social and environmental risk factors include impaired parent–child relationship, bullying, living outside of the home, social isolation, difficulties in school, neither working nor attending school, and presence of stressful life events, such as romantic difficulties or an argument with a parent. Protective factors could be listed as; religious involvement and connection between the adolescent and parents, school, and friends (8).

Gender

Several studies showed that the prevalence of suicide attempts is greater in girls than boys with a ratio varies between 3/1 and 9/1 (8-10). Differences in hormonal and neurotransmitter levels between men and women could be the affecting factors. Impulsive behavioral disorders due to decrease in serotonin levels are more common in women (11). Moreover, hormonal changes during menstrual cycles increase the tendency to suicide in women. In some studies, FSH, LH, estrogen and progesterone were found to be lower than normal population in women who attempted suicide (12,13).

Although suicide attempts are more common in women, completed suicide is 3 times more common in men (8). According to Turkish Statistical Institute 2015 data, 72.7% of the completed suicide cases were men and 27.3% were women (7). During the act of suicide, males generally

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use more violent and lethal methods such as sharp instruments, firearms or hanging, while females mostly prefer methods such as taking drugs or jumping from high (14,15). It is argued that males are more determined to die so they prefer much more lethal methods (15).

Age and Age Range

Suicidal behavior is rare before age of 12 but increases in prevalance through adolescence. The lower frequency of suicidal behavior before adolescence is explained by the inability of children to fully acquire the cognitive maturation that would enable them to plan and perform a suicidal attempt (16). The highest risk period in adolescence is the age of 14-16 years (3,17). In several studies conducted in different provinces of Turkey, the average age of suicide attempt was found to be 14.7 and 16.08 years (9,17,18). As the middle adolescence is the complex period when most of the biological and psychological changes occur, social expectations can be perceived as pressure and adolescents can choose suicide as an escape route from their problems (19).

Education Status

According to Turkish Statistical Institute data, in the last ten years, primary school graduates constituted the highest rate of suicide cases (7). It is considered that, failure to attend school facilitates the suicidal tendency and individuals with low education level are more prone to suicide attempts (2,9). In accordance with this hypothesis, Kesebir et al. (20) revealed that individuals with low education level had less suicide attempt but preferred more lethal suicide methods comparing to those with higher education level.

Personal and/or Parental Mental Disorders

While the individual tries to cope with stressful life events during adolescence, mental diorders such as depression, affective and anxiety disorders may occur (16). The rate of depression in the middle and late adolescence period is between 4-20% and there is a strong relationship between depression and suicide attempt (21). It was shown that, mental disorders are the leading causes of suicide and an individual with major depression has a 20-30 times greater risk of suicide than the general population (20-22).

Considering the underlying causes of depression in adolescence, the most prominent causes are family problems, parental separation, presence of a psychiatric disorder in a family member, school failure, and chronic illness (9,10). Studies on adolescents who attempted suicide showed that anger and impulsivity were more common than the healthy adolescents (9). Yalaki et al. (10) showed that 86.8% of the adolescents who had a previous diagnosis of psychiatric disorder, were showing depressive symptoms during the period when they attempted suicide. Moreover, depressive symptoms were also observed in the mothers of 73.7% of adolescents diagnosed with psychiatric disorders. These results revealed that depressive symptoms of the adolescent and/or a family member and problems within the family would affect each other. It was claimed that approximately 2-3% of adolescents received medical care after suicide attempt, less than 50% had psychotherapy after intervention in emergency services, and most of those who started treatment did not complete their treatment (23). Ekici et al. (24) showed that the presence of physical illness and insufficient dose of psychiatric treatment are two important risk factors for completed suicide. Another study, reported that 15%-21% of the cases had stated that they would attempt suicide again (25). Therefore, regular psychiatric follow-ups of these individuals are required. For the ones who cannot be reached for follow-ups should be contacted and informed about the seriousness of the situation and these individuals should have psychiatric treatment.

Family Effects

Parental separation, presence of suicidal attempts in family members, or family history of psychiatric disorder were shown as important risk factors for suicide (26,27). Many studies showed that, the parents of adolescents with suicidal behavior had lower education levels and the rate of psychiatric disorder presence in a family member was higher compared to normal population (10,28)

History of Physical or Sexual Abuse

It has been reported that sexual or physical abuse during childhood and adolescence increases the risk of suicide throughout life (8,29,30). In a large sampled survey study examining the relationship between abuse and self-harming behavior in high school students in Turkey, it was determined that 34.8% of adolescents had been exposed to trauma, 10.7% had been sexually abused and 25.2% of the cases subjected to sexual abuse had a history of suicide attempt (31). The brutality of sexual harassment can also have an effect on suicidal behavior. Evans et al. (32) revealed that, the rate of suicide attempt was 3.3% in cases with non-contact sexual abuse history, 8.3% in involving touching, and 15.2% in abuse involving sexual intercourse.

School Related Factors

School failure emerges as an important reason for both suicide attempt and adolescent depression (10). Eskin et al. (33) found that 25.7% of 966 high school students had thought of suicide at least once. In another study, it was revealed that the source of psychological problems in high school students who attempted suicide was the anxiety of failing the university exam (16). Ozfirat et al. (34) revealed that 64.2% of the senior high school students with school failure and 36.8% of successful students showed depressive symptoms.

Internet Use

Copycat suicide is an imitative suicidal behaviour that occurs after exposure to another suicide. Increases in internet news and social network services in recent years have provided a highly connected matrix whereby provocative news articles, including reports of celebrity suicide, can travel rapidly and widely (35). It was reported that exposure to suicidal news, describing suicidal methods or relevant contents through television or social media, affect adolescents more than adults, and also causes cluster-style suicidal behavior around them (8,36). Daily use of Internet and video games exceeding 5 hours was strongly associated with higher levels of depression and suicidality (ideation and attempts) in adolescents and suicide-related Internet searches were found to be associated with completed suicides among young adults (8,37).

Nonsuicidal Self-Injury (NSSI)

Nonsuicidal self-injury (NSSI) is defined as repeating, self-harming behaviours which do not include intention to die, and risk of death is deliberately low. Nonetheless, NSSI is a risk factor for suicide attempts and suicidal ideation. In the first 6 months after NSSI, the risk of suicide was found to be very high, and was mentioned that the risk continued later (38).

Lesbian, Gay, Bisexual, Transgender, and Questioning (LGBTQ) Adolescents

Lesbian, gay, bisexual, transgender, and questioning (LGBTQ) adolescents experience higher rates of substance use, risky sexual behaviors (HIV, sexually transmitted infections, unintended pregnancies) and suicidal attempts. Stigma and minority stress processes are the major theorized causes of this negative health outcomes experienced by LGBTQ populations. These stressors activate a physiological stress response, which can affect the mental and physical health of stigmatized populations, and lead to suicidal attempts (39). Risk factors and causes of suicide in LGBTQ population can differ according to age or type of sexual orientation. In a study about LGBTQ suicides, it was found that 12- to 17-year-olds had a 3.6 times more suicidal attempts than 18- to 29-year-olds and cases of gay males, bisexual males and bisexual females were particularly likely to include family/peer rejection and bullying as contributing circumstances, while lesbians' cases more often mentioned romantic breakups (40)

Suicide Ideation and Attempts During The Covid 19 Pandemic

In many reports, elevated rates of mental health concerns have been identified during the COVID-19 pandemic. Due to restrictions and lock downs, greater levels of negative COVID-19 experiences were associated with increased depressive symptoms and anxiety among adolescents (41). Results from a emergency service study indicated a significantly higher rate of suicide ideation in March and July 2020 and higher rates of suicide attempts in February, March, April, and July 2020 as compared with the same months in 2019 among youth aged 11 to 21 (42).

FEATURES OF SUICIDE

Time of Suicide

There are many studies investigating on the effects of climate conditions on suicide and these studies revealed that the time of suicide varied according to the region, season or the province of the study (43-48). The studies conducted in Turkey among adolescents showed that suicide attempts were increasing in summer, during the closing period of schools, where the peak was seen in spring or winter months (45-47). It is thought that, decrease in school success among adolescents, especially during school closure periods, constitutes a risk factor for suicide attempts (47,48). In addition, stress of the exams and as warming of the weather, romantic breakups can be shown as the reasons for an increase in suicide attempts in spring and summer months (49).

Hour and Location of Suicide

The suicide hour varies according to the age, determination of the individual and the choice of method (48). It has been stated that, majority of the adolescents attempts suicide between 18.00-24.00 hours (48,49). The main purpose of suicidal attempts without the idea of death is to attract the attention of parents or friends, to show problems that cannot be solved; briefly to call for help. For this reason, evening hours are preferred by adolescents more frequently when the family members can interfere with them (48). In contrast, Taktak et al. (50) showed that the completed suicide attempts usually (70.2%) occured during the day time. It was also suggested that adolescents mostly choose the evening hours when they are not active and alone, and the most preferred places for suicide attempts are their homes (50,51).

Methods of Suicide

The determination for death affects the chosen method. Adolescents generally attempt suicide due to their impulsiveness (47). By suicide attempt they express themselves to seek help or take attention rather than desire to die (18,47). It was shown that, the most common method in suicide attempts in adolescence is drug intake (52,53). However, in completed suicides, the most common methods have been reported as suffocation, firearm, poisoning and high jump (8). The most preferred drugs are the frequently available or can be easily obtained drugs at home such as analgesics/anti-inflamatory drugs, antidepressants, antipsychotics, antibiotics, cardiac and stomach drugs (10,52,54).

Preventing Adolescent Suicides

Along with all information, unfortunately, suicide is not an accurately predictable situation but health care professionals can only determine who is at higher risk. Intent is a major key in the determination of risk. Adolescents at high risk are those with a plan or recent suicide attempt with a high probability of lethality; stated current intent to die, recent suicidal ideation or agitation, impulsivity or severe hopelessness; or profoundly dysphoric mood associated with bipolar disorder, major depression, psychosis, or a substance use disorder (8). Therefore, pediatricians should screen adolescents for suicidal thoughts, mood disorders, and alcohol/drug abuse in their visits. Suicidal ideation may be assessed by directly asking questions or screening via self-reports. Self-administered scales can be useful because adolescents may disclose information about suicidality on self-reports which they deny in conversation (8).

It is always necessary to understand nonsuicidal self-injury (NSSI) and suicide attempts as the adolescent has a dilemma and they should be referred for help. If the adolescent has ever had at least one NSSI behaviour, she/he should be consulted to adolescent psychiatry and follow-up visits should be conducted in collaboration. The most important point in treatment is to prevent external factors that push the patient to NSSI and suicidal attempt and to increase the adolescent's ability to cope with stress, solve problems, control their emotions and impulsivity. If there is a concomitant psychiatric illness, it should be treated by medication and/or psychotherapy (38). Among the antidepressants, fluoxetine is formally approved by the Food and Drug Administration (FDA) for treating depression in pediatric patients and sertraline, fluvoxamine, and clomipramine are approved for treating obsessive-compulsive disorder (OCD) in children and youth (55). Lithium, with antimanic and antidepressant effects, is the gold standard mood-stabilising agent for the treatment of adolescents with bipolar disorders, and has anti-suicide effects (56).

The FDA recommends that a child receiving anti depressants should visit the prescribing physician once a week for the first four weeks of treatment; biweekly for the second month of treatment; and at the end of the 12th week on medication (55). Along with the treatment, adolescents should be supported to participate in volunteer services to assist people in need of help, participate in social, creative and sports activities and/or artistic courses with peers. All this will allow the adolescent to gain self-confidence and positive self-perception and will also give the adolescent the ability to cope with external difficulties (8,38).

There are many suicide prevention efforts all around the World that focused on school education programs, crisis center hotlines, media guidelines (suicide prevention strategies that involve educating media professionals about the prevalence of copycat suicides among adolescents, in an effort to minimize the impact of news stories reporting suicide) and efforts to limit firearm access (57). Morken et al. (58) suggest that school-based interventions prevent suicidal ideation and attempts in the short term, but prevent suicide attempts in the long term. Considering that adolescents are in the high-risk group of suicide attempts, it is very important to generalize school health services and adolescent health units in preventing these attempts so WHO has mostly focuses on school education programs to prevent suicide (59).

It should be known that before suicide attempt, many cases convey their suicidal thoughts directly or indirectly to their friends and families. Informing students about signs and symptoms associated with suicide would help them to notice the current symptoms and could explain to their friends. It is believed that the inclusion of training programs with presentations, video screenings, activities and discussions on behavioral disorders, violence, abuse and suicide in the National Education Curriculum of the high school students, could be protective (2). World Health Organisation (WHO) focuses on school-base interventions to prevent adolescent suicide attempts. They recommend: Strengthening the mental health of schoolteachers and other school staff, strengthening students' self-esteem, promoting emotional expression, preventing bullying and violence at school, providing information about care services, communication and improving school staff's skills to prevent suicide among adolescents (59).

In Turkey, a pilot programme titled "Psychosocial Support and Intervention of Crisis Program for Suicide Attempts in Emergency Service" was initiated by the Ministry of Health Department of Mental Health and has been implemented in 32 provinces in 2004. The aim of this program was to record suicide attempts in emergency services and to create a database. Moreover, in suicidal attempt cases, the programme provides the adolescents and their families psychosocial support. It was planned to create a surviallance by filling out the "suicide attempt feedback form" for the cases recorded as suicidal attempt. After initial evaluation and intervention at the emergency service, they are referred to the psychosocial support unit, then after, cases deemed necessary were consulted with psychiatry. Relatives of the patients were included in this process when it is necessary (60).

CONCLUSION

Adolescent suicide is an important public health problem. The causes include psychological, environmental and social factors, and mental disorder is the leading risk factor for suicide. Suicide risk factors vary with age, gender, family dynamics and stressful life events. Although there are some possible warning signs, it is difficult to accurately predict which persons with these risk factors will ultimately commit suicide. As we are pediatricians who follow adolescents in our clinics, we should be aware of risk factors, regularly screen adolescents and do collaborative safety planning for suicidal patients.

ETHICAL DECLARATIONS

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REFERENCES

1. Weis M: Suicide. In: S. Arieti (ed). A Handbook of Psychiatry. Newyork: Basic Books Inc; 1974: 743-65.
2. Bilginer Ç, Çöp E, Göker Z, Hekim Ö, Sekmen E, Üneri Ö. İlaç içerek intihar girişiminde bulunan gençler ve koruyucu-önleyici hizmetlere genel bakış. Dusunen Adam J Psychiatry Neurol Sci 2017; 30: 243-50
3. Özgüven Devrimci H, Sayıl I. Suicide attempts in Turkey: Results of the WHO-EURO multicentre study on suicidal behaviour. Can J Psychiatry 2003;48: 324-9
4. CDC, National Center for Health Statistics, Adeolescent Health, https://www.cdc.gov/nchs/fastats/adolescent-health.htm (Access March 20, 2021)
5. Ayas S, İşsizlik ve eğitim seviyesinin intihar üzerindeki etkisi: TÜİK verileri üzerine ampirik bir çalışma. Yönetim Bilimleri Derg / J Administrative Sci 2016; 14: 101-19.
6. Bilici M, Bekaroglu M, Hocaoglu C et al. Incidence of completed and attempted suicide in Trabzon, Turkey. Crisis 2002; 23: 3-10.
7. Türkiye İstatistik Kurumu (TUİK), Türkiye İntihar İstatistikleri, 2015, http://www.tuik.gov.tr (Access August 8, 2017)
8. Shain B. Committee on adolescence, suicide and suicide attempts in adolescents. Pediatrics 2016; 138: e20161420
9. Akin E, Berkem M. İntihar girişiminde bulunan ergenlerde öfke ve dürtüsellik. Marmara Med J 2012; 25:148-52
10. Yalaki Z, Çakır İ, Taşar M, Yalçın N, Bilge Y. Anne ve ergenlerdeki depresif belirtilerin ergen intiharları ile ilişkisi. Dicle Med J 2012; 39: 350-8.
11. Nock MK, Borges G, Bromet EJ, et al. Suicide and suicidal behavior. Epidemiol Rev 2008; 30: 133-54.
12. Kim B, Kang ES, Fava M, et al. Follicle-stimulating hormone (FSH), current suicidal ideation and attempt in female patients with major depressive disorder. Psychiatry Res 2013; 210: 951-6.
13. Baca-Garcia E, Diaz-Sastre C, Ceverino A, et al. Suicide attempts among women during low estradiol/low progesterone states. J Psychiatr Res 2010; 44: 209-14.
14. Carroll-Ghosh T, Victor BS, Bourgeois JA, Suicide. In: Hales RE, Yudofsky SC (eds) Textbook of Clinical Psychiatry, 4th edition. Washington DC: The American Psychiatric Publishing 2003: 1457-83.
15. Eskin M, Albuharian F, Rezaeian M, et al. Suicidal thoughts, attempts and motives among university students in 12 muslim-majority countries. Psychiatry Q 2019: 90; 229-48.
16. Hawton K, Saunders KE, O'Connor RC. Self-harm and suicide in adolescents. Lancet 2012; 379: 2373-82.
17. Yektaş Ç, Bildik T, Özbaran NB, Köse S, Erermiş S. Depresif kiz ergenlerde intihar davranişinin klinik özellikleri. Çocuk ve Gençlik Ruh Sağlığı Derg 2014; 21: 33–44.
18. Çelik G, Yıldırım V, Metin Ö. Özkıyım girişimi olan ergenlerde ruhsal bozukluklar, benlik ve aile işlevselliği. Anatolian J Psychiatry 2011; 12: 280-6.
19. Sayar K, Öztürk M, Acar B. Aşırı dozda ilaç alımıyla intihar girişiminde bulunan ergenlerde psikolojik etkenler. Klinik Psikofarmokoloji Bülteni 2000; 10: 133-8.
20. Kesebir S, Gülpek D, Noyan MA. Özkıyım girişimlerinin doğası, Anadolu Psikiyatri Derg 2002; 3: 88-94.
21. Eskin M. Lise öğrencisi ergenlerde depresyonun yaygınlığı ve ilişkili olduğu etmenler. Türk Psikiyatri Derg 2008; 19: 382-9.
22. Aydemir Ç, Vedin TH, Göka E. Major depresyon ve özkıyımda kognitif ve emosyonel faktörler. Türk Psikiyatri Derg 2002; 13: 33-9.
23. Köse A, Eraybar S, Köksal Ö, Patients over the age of 15 years admitted for attempted suicide to the emergency department and the psychosocial support unit. JAEM 2012; 11: 193-6.
24. Ekici G, Savaş HA, Çıtak S. Tamamlanmış intiharlarda iki önemli risk etmeni: fiziksel hastalığın varlığı ve yetersiz dozda psikiyatrik tedavi, Klinik Psikofarmakoloji Bülteni, 2001; 11: 168-9.
25. Hvid M, Vangborg K, Sorensen HJ et al. Preventing repetition of attempted suicide-II. The Amager Project, a randomized controlled trial. Nord J Psychiatry 2010; 65: 292-8.
26. Mittendorfer-Rutz E, Rasmussen F, Lange T. A life-course study on effects of parental markers of morbidity and mortality on offspring's suicide attempt. PLoS ONE 2012; 7: e51585.
27. Akbas S, Boke O, Karabekiroğlu K, et al. Hastane başvurusu intihar girişimi ile olan ve olmayan depresif çocuk ve ergenlerin ayırt edici özellikleri. Türkiye'de Psikiyatri 2008;10:2
28. Güleç G, Aksaray G. İntihar girişiminde bulunan gençlerin sosyodemografik sosyokültürel ve aile özelliklerinin araştırılması. Yeni Sempozyum 2006; 44:3
29. Bebbington PE, Cooper C, Minot S, et al. Suicide attempts, gender, and sexual abuse: data from the 2000 British Psychiatric Morbidity Survey. Am J Psychiatry 2009; 166: 1135-40.
30. Wong WH, Kuo WH, Sobolewski C, Bhatia I, Ip P. The association between child abuse and attempted suicide. Crisis 2020; 41:196-204.
31. Zoroğlu SS, Tüzün Ü, Şar V, Öztürk M, Kora ME, Alyanak B. Çocukluk dönemi istismar ve ihmalinin olası sonuçları. Anadolu Psikiyatri Derg 2001; 2: 69-78.
32. Evans E, Hawton K, Rodham K. Suicidal phenomena and abuse in adolescents: a review of epidemiological studies. Child Abuse & Negl 2005; 29: 45–58.
33. Eskin M. Gender and cultural differences in the 12- month prevalence of suicidal thoughts and attempts in Swedish and Turkish adolescents. Journal of Gender, Culture and Health 1999; 4: 187-200.
34. Özfirat Ö, Pehlivan E, Özdemir F. Malatya il merkezindeki lise son sınıf öğrencilerinde depresyon prevalansı ve ilişkili faktörler. İnönü Üniversitesi Tıp Fakültesi Derg 2009; 16: 247-55.

35. Yi H, Hwang J, Bae HJ, Kim N. Age and sex subgroups vulnerable to copycat suicide: evaluation of nationwide data in South Korea. Sci Rep 2019; 9: 17253.

36. Copeland WE. Editorial: One Reason Why Not. J Am Acad Child Adolesc Psychiatry 2020; 59: 216-8.

37. Messias E, Castro J, Saini A, Usman M, Peeples D. Sadness, suicide, and their association with video game and internet overuse among teens: results from the youth risk behavior survey 2007 and 2009. Suicide Life Threat Behav 2011; 41: 307–15

38. Birinci basamak sağlık çalışanları için ergen sağlığına ve sorunlarına yaklaşım cep kitabı, 2017; 42-3, https://kirklareliism.saglik.gov.tr/Eklenti/115480/0/birinci-basamak-saglik-calisanlari-icin-ergen-sagligina-ve-sorunlarina-yaklasim-cep-kitappdf.pdf (Access March 8, 2021)

39. Johns MM, Poteat VP, Horn SS, Kosciw J. Strengthening our schools to promote resilience and health among LGBTQ youth: emerging evidence and research priorities from The State of LGBTQ Youth Health and Wellbeing Symposium. LGBT Health 2019; 6: 146-55.

40. Ream, GL. An investigation of the LGBTQ+ youth suicide disparity using national violent death reporting system narrative data. J Adolescent Health 2020; 66: 470-7.

41. Mamun MA, Sakib N, Gozal D, Bhuiyan AI, Hossain S, Bodrud-Doza M et al. The COVID-19 pandemic and serious psychological consequences in Bangladesh: A population-based nationwide study. J Affect Disord. 2021; 279: 462-72.

42. Hill RM, Rufino K, Kurian S, Saxena J, Saxena K, Laurel Williams. Pediatrics. 2021;147:e2020029280.

43. Christodoulou C, Efstathiou V, Bouras G, Korkoliakou P, Lykouras L. Seasonal variation of suicide. Encephalos 2012; 49:73-9.

44. Çam B, Karlıdere T, Aytekin S. İntihar girişimi, sosyodemografik özellikler ve mevsimsellik. Klinik Psikofarmakoloji Bülteni 2012; 22: 158.

45. Şevik AE, Özcan H, Uysal E. İntihar girişimlerinin incelenmesi: Risk faktörleri ve takip. Klinik Psikiyatri Derg 2012; 15: 218-25.

46. Günderci A, Karatay G, Tunceli' de 2005-2015 yılları arasında gerçekleşen intiharlara ilişkin epidemiyolojik bir inceleme, Klinik Psikiyatri 2017; 20: 121-8.

47. Görücü A, Eraslan R, Göker Z. Dürtüsel Nitelikteki Özkıyım Girişiminde Mevsimin Etkisi: Tanımlayıcı Bir Çalışma. Türkiye Çocuk Hastalıkları Derg 2020; 1-6.

48. Johnson GR, Krug G, Potter LB, Suicide among adolescents and young adults: A cross-national comparison of 34 countries. Suicide and Life-Threatening Behavior 2000; 30: 74-82.

49. Söğüt Ö, Sayhan M, Gökdemir M. Türkiye'nin Güneydoğusunda, Şanlıurfa ve Çevresinde Özkıyım Girişimlerinin Değerlendirilmesi, JAEM 2011; 8-13.

50. Taktak Ş, Üzün İ, Balcıoğlu İ. İstanbul'da tamamlanmış intihar olgularının psikolojik otopsisi, Anadolu Psikiyatri Derg 2012; 13: 117-24.

51. Yalaki Z, Taşar MA, Yalçın N, Dallar Y. Çocukluk ve gençlik dönemindeki özkıyım girişimlerinin değerlendirilmesi, Ege Tıp Derg 2011; 50: 125-8.

52. Miniksar Ö, Yıldız Miniksar D. Yoğun bakım ünitesinde takip edilen ergen ilaç intoksikasyonların retrospektif değerlendirilmesi. J Health Sci Med 2020; 3: 203-8.

53. Eaton D.K. Youth Risk Behavior Surveillance -United States, 2011. Morbidity and Mortality Weekly Report 2012; 61.

54. Güloğlu C, Gökhan Ş, Üstündağ M, Orak M. Acil servise başvuran olguların kullandıkları yöntemler ve demografik verilerinin mortalite ile ilişkisi. Türkiye Acil Tıp Derg 2009; 9: 109-14.

55. American Psychiatric Association and American Academy of Child and Adolescent Psychiatry. The use of medication in treating childhood and adolescent depression: information for physicians. www.parentsmedguide.org/physiciansmedguide.pdf. (Access April 2, 2021)

56. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. Lancet 2020; 396: 1841-56.

57. Teen Suicide is Preventable, American Psychological Association https://www.apa.org/research/action/suicide (Access: July,10,2021)

58. Morken IS, Dahlgren A, Lunde F, Toven S. The effects of interventions preventing self-harm and suicide in children and adolescents: an overview os systematic review. F1000Research 2020; 8: 890.

59. WHO Preventing suicide A Resource for teachers and other school staff. https://www.who.int (Access: July 10, 2021)

60. Acil Serviste İntihar Girişimlerine Psikososyal Destek ve Krize Müdahale Programı, Sağlık Bakanlığı, Temel Sağlık Hizmetleri Genel Müdürlüğü, Ruh Sağlığı Daire Başkanlığı,2004 http://www.istanbulsaglik.gov.tr/w/sb/halksag/belge/mevzuat/acilde_intihar_girisim_psiko_destek_kriz_muda_prg.pdf (Access October 10, 2020)

Case Report

HEALTH SCIENCES
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Acute aortoiliac occlusion in a COVID-19 patient

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ABSTRACT

Although COVID-19 patients are usually seen with respiratory system symptoms, these patients may also display different symptoms. COVID-19 has been associated with a variety of prothrombotic diseases such as myocardial infarction and stroke. However, the pathogenesis of this hypercoagulation has not yet been fully clarified. In this report, we present a COVID-19 patient who admitted with the complaint of weakness in both legs and was then diagnosed with aortoiliac occlusion.

Keywords: Acute arterial thrombosis, acute limb ischemia, aortic occlusion, hypercoagulability, COVID-19

INTRODUCTION

A new type of coronavirus disease (COVID-19)—which first emerged in Wuhan, China—has become a major world pandemic causing serious morbidity and mortality throughout the world (1-4). Although the relationship between severe COVID-19 infection cases and venous thromboembolism has been described in the literature (5,6), few cases have been reported for arterial thrombosis (7). Here, we present a case of acute aortoiliac occlusion in a COVID-19 infected patient.

CASE REPORT

A 65-year-old male patient admitted to the emergency department with the complaint of weakness in both legs that had started three hours before. The patient, who also had heart failure and hypertension, and reported that he used enalapril 10 mg, spironolactone 25 mg, and furosemide 80 mg, daily. He reported neither previous lower limb claudication nor arterial or venous thromboembolism. The patient stated that he had visited another hospital with the complaint of a dry cough, 10 days before when his coronavirus test was found positive. He isolated himself at home and used favipiravir for 5 days (600 mg daily for 5 days following a single loading dose of 1600 mg on the 1st day). Vital signs at the time of admission were recorded: fever 37.0°C; blood pressure 165/77 mmHg; heart rate 65/min; and sO2 at room air 93%. The patient's body mass index was calculated as 22.4. A physical examination revealed bilateral acute lower limb ischemia along with tachypnea. The electrocardiogram was normal. The coagulability workup (including aPTT, PT, INR, fibrinogen) and other laboratory results were normal, except for a C-reactive protein (CRP) level of 103 mg/L (normal range:0-5) and a D-dimer level of 860 ng/mL (<250 ng/mL). A chest computed tomography (CT) demonstrated diffuse bilateral consolidation (**Figure 1**). The CT angiography showed acute thrombotic occlusion in the infrarenal aorta extending to the common iliac arteries (**Figure 2**). The transthoracic echocardiogram did not reveal any potential source of embolism. Anticoagulant therapy was not given to the patient before thromboembolectomy. Percutaneous mechanical thromboembolectomy was performed in the emergency operating room and significant clinical and radiological improvements were achieved. The patient was hospitalized for routine post-operative care and COVID-19 treatment. The patient was discharged on the 12th day of hospitalization without any sequelae.

DISCUSSION

Coronavirus creates a prothrombotic condition in infected hosts. Thrombotic complications in COVID-19 patients can emerge in a variety of ways including venous thromboembolism and ischemic complications associated with thrombosis of the limb, cerebral, coronary, and visceral arteries. Findings suggest that endothelial dysfunction, inflammation, cytokine release, hypercoagulation, and hypoxia contribute to thrombosis (8).

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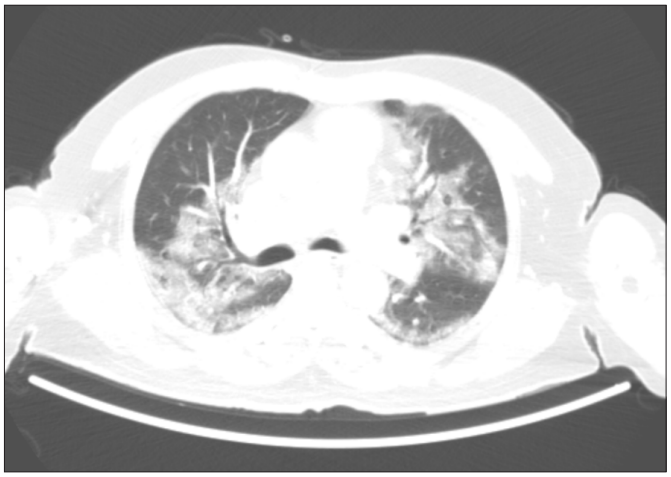

Figure 1. Chest CT scan showing pulmonary lesions typical of COVID-19.

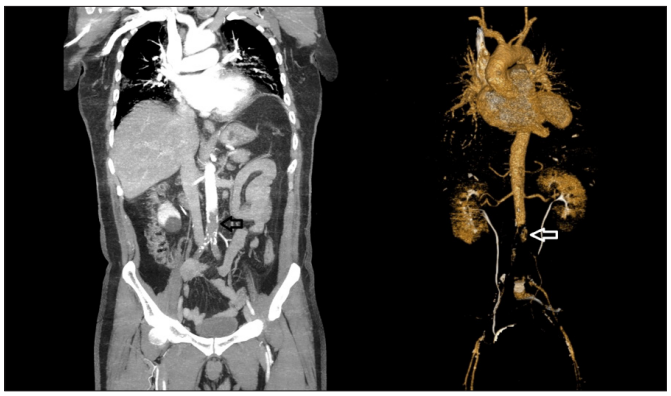

Figure 2. Infra-renal distal aortic and left iliac artery thrombotic occlusion on CT angiography, 3-dimensional reconstruction (arrows).

In the literature, as in this case, reports show a relationship between a coronavirus infection and lower limb arterial thrombosis, such as aortoiliac thrombosis. Vulliamy et al. (9) reported two patients with COVID-19 pneumonia who also had acute thrombotic occlusion of the descending aorta. Bellosta et al. (10) published a descriptive cohort study involving 20 Italian patients with acute arterial ischemia. In their study, they proposed a virus-associated hypercoagulation as a possible etiology. Klok et al. (11) reported a 31% incidence rate of arterial or venous complications in 184 COVID-19 patients in intensive care units (ICU). In this cohort, 65 with pulmonary embolism, 3 with deep venous thrombosis, 5 with ischemic strokes, and 2 with systemic arterial thromboembolism were reported. Perini and colleagues reported 4 COVID-19 patients who had acute limb ischemia (ALI) symptoms. Two of these patients had no previously known underlying health conditions or risk factors. One of these patients was a 53-year-old male who not only showed symptoms of ALI but also signs of acute aortoiliac occlusion. This patient underwent an open thrombectomy but on the second postoperative day the patient died (12).

Prophylactic anticoagulation therapy is recommended for hospitalized patients with COVID-19 (13,14). In our case study, the only treatment the patient received for the COVID-19 infection was favipiravir. However, prophylactic anticoagulants should also be given to outpatients who are elderly and have comorbidity (14).

CONCLUSION

As COVID-19 cases continue to increase globally, the number of patients with arterial thrombosis is inevitable. Since these patients are kept under strict isolation protocols, it is necessary to be vigilant towards this complication since it requires such rapid intervention. As in our case, COVID-19 patients who have arterial thrombosis could be successfully treated with anticoagulation and emergency intervention. Early recognition and intervention of ALI—which leads to a sudden reduction in limb perfusion—can help maximize the chances of limb salvage and reduce the risk of mortality among patients. When linked to COVID-19, the early recognition of this complication offers a higher probability of an improved outcome.

ETHICAL DECLARATIONS

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

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Rohat AK., Doğanay F. Relationship between mean platelet volume and intensive care unit requirement in COVID-19 patients. J Health Sci Med 2021; 4: 353-7.
2. Seyhan AU, Doganay F, Yilmaz E, Topal N P, Ak R. Investigation of QT prolongation with hydroxychloroquine and azithromycin for the treatment of COVID-19. J Coll Physicians Surg Pak 2021; 30: 153-7.
3. 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.
4. Ak R, Kurt E, Bahadirli S. Comparison of 2 risk prediction models specific for COVID-19: the brescia-COVID respiratory severity scale versus the quick COVID-19 severity index. Disaster Med Public Health Prep 2021; 1-5.

5. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Col Cardiol 2020; 75: 2352-71.

6. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J 2020; 41: 1858-8.

7. Levolger S, Bokkers RP, Wille J, Kropman RH, De Vries JPP. Arterial thrombotic complications in COVID-19 patients. J Vasc Surg Cases Innov Tech 2020; 6: 454-9.

8. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. The Lancet 2020; 395: 1417-8.

9. Vulliamy P, Jacob S, Davenport RA. Acute aorto-iliac and mesenteric arterial thromboses as presenting features of COVID-19. Br J Haematol 2020; 189: 1053-4.

10. Bellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020; 72: 1864-72.

11. Klok FA, Kruip MJHA, Van der Meer NJM, et al. H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145-7.

12. Perini P, Nabulsi B, Massoni CB, Azzarone M, Freyrie A. Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19. The Lancet 2020; 395: 1546.

13. Topcu AC, Ozturk-Altunyurt G, Akman D, Batirel A, Demirhan R. Acute Limb Ischemia in Hospitalized COVID-19 Patients. Ann Vasc Surg 2021; S0890-5096(21)00233-8.

14. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol 2020; 189: 846-7.

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