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Our dear readers,

We are happy to publish the new issue of our journal. JHSM has completed 5 years since its establishment. When we look at these five years, it is clearly understood that our journal has come a long way in a positive way. We are getting closer to our scientific goals day by day. As we mentioned before, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering valuable international indexes such as SCI-Exp and Pubmed. We 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.

Sincerely yours

Alpaslan TANOGLU, MD, PhD
Editor-in-Chief

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Platelet-to-lymphocyte ratio and mean platelet volume-to-platelet count ratio for predicting mortality in critical COVID-19 patients

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ABSTRACT

Introduction: Defining the markers that can be used in clinical practice for predicting the mortality of critical patients will be cautionary for taking necessary measures in high-risk cases. Although there are a large number of studies conducted during the pandemic, no mortality marker to predict the prognosis of intensive care unit (ICU) patients with COVID-19 has yet been defined. Platelet indices can be easily evaluated with a complete blood count (CBC) analysis, one of the most accessible tests worldwide. This study aimed to evaluate the role of platelet indices such as mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), platelet-to-lymphocyte ratio (PLR), and MPV-to-platelet count ratio (MPV/PLT) in predicting the mortality of ICU patients with COVID-19.

Material and Method: This single-center, retrospective, cross-sectional study included 201 critical COVID-19 patients over 18 years of age who were hospitalized in ICU between August 2020 and February 2021. Patients were divided into two groups as survivors and non-survivors. The relationship of MPV, PDW, PCT, PLR, and MPV/PLT parameters evaluated at ICU admission with mortality was investigated.

Results: There was no significant difference between the survivor and non-survivor groups in terms of platelet count, MPV, PCT, and PDW. The comparison of the platelet ratios revealed higher PLR and MPV/PLT ratio in the non-survivor group than in the survivor group ($p<0.05$). The cut-off value of PLR for predicting mortality was found to be 292.20 (AUC: 0.601 [95% CI 0.522-0.681]) ($p<0.05$), while the cut-off of MPV/PLT was found to be 0.0289 (AUC: 0.590 [95% CI 0.510-0.671]) ($p<0.05$).

Conclusion: The results of this study demonstrated PLR and MPV/PLT ratio were associated with mortality. The use of ratios such as MPV/PLT and PLR as an early prognostic indicator instead of platelet indices alone, like MPV in ICU patients with COVID-19, may help identify high-risk patients early.

Keywords: COVID-19, mortality, PLR, MPV/PLT, intensive care

INTRODUCTION

The COVID-19 pandemic, which started in February 2020, has been affecting the world for more than two years. Although the number of cases has decreased with the measures and vaccination studies, the effects of the pandemic still continue today (1). During this period, a large numbers of severe COVID-19 cases were followed in intensive care units (ICU) around the world.

Numerous studies have been conducted to identify severe cases, determine hospitalization criteria, predict prognosis, and investigate various laboratory examinations (2,3). These studies have mainly evaluated patients treated in emergency departments and outpatient clinics with high patient density. Studies on ICU patients have focused on determining the criteria for admission to the ICU. Although many parameters have been studied, a specific mortality marker to predict the prognosis of critically ill ICU patients with COVID-19 has not yet been defined. While studies have emphasized inflammatory markers since the disease causes systemic inflammation, there are studies conducted with various markers such as pro-inflammatory cytokines, C-reactive protein (CRP) and ferritin (4-6). Even though the relationship of the

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studied markers with the disease is significant with high specificity and sensitivity, the tests to be used in pandemics affecting the whole world must be easily accessible and cost-effective in clinical practice. Complete blood count (CBC) is an inexpensive test that produces rapid results and can be easily accessed in all hospitals. It is known that viral diseases such as COVID-19 lead to changes in hematological parameters. Lymphopenia is common in viral infections, and studies have shown the relationship between disease severity and depth of lymphopenia. Many parameters can be evaluated in a single CBC analysis; however, studies using CBC in cases of COVID-19 have generally focused on lymphocyte levels (7).

Although platelets are mainly responsible for hemostasis, they affect the immunomodulatory system. There are studies investigating platelet count and platelet indices to predict prognosis, especially in viral infections and non-COVID-19 critically ill patients with sepsis (8). Studies evaluating the role of platelet count and platelet indices in predicting the prognosis of COVID-19 cases have generally investigated outpatients or patients hospitalized in the ward (9). It has been reported that platelet indices, including mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), platelet-to-lymphocyte ratio (PLR), and MPV-to-platelet count ratio (MPV/PLT) are more sensitive than platelet count for predicting prognosis in critically ill patients (10,11). Although studies have been conducted to evaluate platelet count in adult ICU patients with COVID-19, there are no ICU studies with large series investigating the relationship between platelet indices, the ratios of these parameters, and ICU mortality.

The effects of the recognition of the disease with numerous studies and the experience of health professionals on the reduced impact of the pandemic and the decreased mortality compared to the initial stage of in the fight against COVID-19 cannot be denied. Therefore, studies on COVID-19 are critical in benefiting from the experience gained during the COVID-19 pandemic in the fight against viral infections in future epidemics.

There are clinical scoring systems that predict mortality in ICU patients. However, a scoring system or mortality marker that has been specifically developed for COVID-19 and is used in clinical practice has not yet been defined. The use of cost effective, easy-to-evaluate markers that can be accessed everywhere for predicting mortality risk and prognosis of critically ill patients will be beneficial in terms of early recognition of these patients and taking necessary measures in clinical practice. This study aimed to evaluate the role of platelet indices MPV, PDW, PCT, PLR, and MPV/PLT, which can be evaluated with CBC, in predicting the mortality of ICU patients with COVID-19.

MATERIAL AND METHOD

This is a single-center, retrospective, cross-sectional study conducted in a tertiary pandemic hospital, in Ankara, Turkey. After obtaining ethics committee approval, all patient data were collected from electronic medical records and patient files (Approval Date: 07.04.2021; Approval Number: 2021/E2-21-358). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included patients over 18 years of age who were hospitalized in the COVID-19 ICU between 1 August, 2020 and 1 February, 2021 and who had a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test result for COVID-19. Patients with comorbidities that could affect platelet indices such as immunodeficiency and hematological disorders, patients on chronic therapies that could affect platelet indices, pregnant womens, and those hospitalized in the ICU for less than 24 hours were excluded from the study. Throughout the study period, 382 patients with COVID-19 were followed up in the ICU. Eighty-eight patients were excluded from the study due to testing negative in RT-PCR, 49 patients due to comorbidities or drug use that could affect platelet indices and 44 patients due to mortality in the first 24 hours of admission. The study included 201 patients who met the inclusion criteria and had complete data. The diagnosis of COVID-19 was made by RT-PCR. In our hospital, the intensive care specialists determine the indication for ICU admission of patients.

Patients' demographic data, comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores, Sequential Organ Failure Assessment (SOFA) scores, and Glasgow Coma Scale (GCS) scores at ICU admission were reviewed. Platelet, lymphocyte, white blood cell and neutrophil counts, MPV, PDW, PCT, neutrophil-to-lymphocyte ratio (NLR), haemoglobin, D-dimer, CRP, procalcitonin, ferritin, interleukin-6 (IL-6), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) measured on the day of ICU admission were recorded. Eventually, the PLR and MPV/PLT ratio were calculated. CBC was performed using the ADVIA 2120 Hematology System (Siemens Healthcare). Mortality rates, invasive mechanical ventilation (MV) requirement, MV duration and ICU length of stay (LOS) were analyzed. Patients were divided into two groups: survivors and non-survivors.

Statistical Analysis: Statistical Package for the Social Science (SPSS) version 25.0 software package was used to analyze the study data. In the study, the continuous variables were presented as median (minimum-maximum) values, while categorical variables were presented as frequency and relative percentage values. Student's t-test or Mann-Whitney U test was used

depending on normality distribution in the inter-group comparison of continuous variables. The chi-square test or Fisher's exact test were used to compare categorical variables. A "Receiver Operating Characteristic (ROC)" analysis was carried out to predict mortality. The area under the curve (AUC), cut-off points, and the sensitivity and selectivity values of these cut-off points were calculated. A p-value <0.05 was considered statistically significant in all analyses.

RESULTS

The study included 201 critically ill ICU patients with COVID-19, with a mean age of 70.00±14.49 years. Of the patients, 72 (35.8%) were female, and 129 (64.2%) were male. The survivor and non-survivor groups were similar in terms of gender distribution. The mean age of the survivor group (62.61±16.23 years) was lower than that of the non-survivor group (71.92±11.48 years) (p<0.05). The most frequent comorbidity in the entire population was hypertension (51.7%). The non-survivor group had higher APACHE-II and SOFA scores and lower GCS scores compared to the survivor group (p<0.05). The median ICU LOS of all patients was 9 (range, 1-56) days. The ICU LOS was 10 (range, 1-56) days in the non-survivor group and 7 (range, 2-39) days in the survivor group, with a significant difference between the two groups (p<0.05). The MV duration was 4 (range, 0-55) days in the non-survivor group, which was longer (p<0.05) compared to the survivor group (**Table 1**). The ICU mortality rate of the entire population was 56.2%.

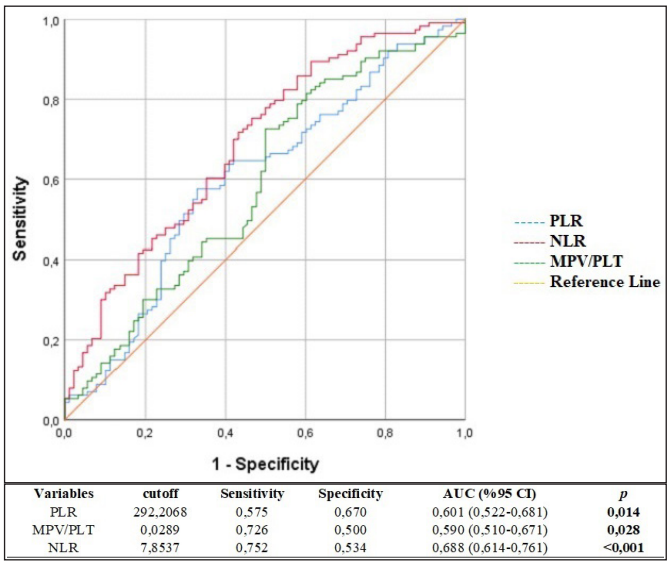
Table 1. Demographic and clinical characteristics of the patients

Variables	All patients (n=201)	Survivors (n=88, 43.8%)	Non-survivors (n=113, 56.2%)	P
Age, y (mean±SD)	70.00±14.49	62.61±16.23	71.92±11.48	<0.001*
Gender n (%)				
Female	129 (64.2%)	60 (68.2%)	69 (61.1%)	0.296
Male	72 (35.8%)	28 (31.8%)	44 (38.9%)	
Comorbidities n (%)				
Hypertension	104 (51.7%)	40 (45.5%)	64 (46.6%)	0.115
Diabetes Mellitus	67 (33.3%)	23 (26.1%)	44 (38.9%)	0.056
COPD	34 (16.9%)	9 (10.2%)	25 (22.1%)	0.041*
Asthma	10 (5.0%)	4 (4.5%)	6 (5.3%)	1.000
CV Disease	72 (35.8%)	26 (29.5%)	46 (40.7%)	0.102
CKD	15 (7.5%)	7 (8.0%)	8 (7.1%)	1.000
CVD	17 (8.5%)	4 (4.5%)	13 (11.5%)	0.133
APACHE II	18 (3-50)	11 (3-42)	25 (9-50)	<0.001*
GCS	15 (3-15)	15 (4-15)	12 (3-15)	<0.001*
SOFA	4 (0-15)	3 (0-10)	8 (3-15)	<0.001*
ICU LOS, days	9 (1-56)	7 (2-39)	10 (1-56)	0.013*
MV duruation, days	1 (0-55)	0 (0-32)	4 (0-55)	<0.001*

* Significant difference at p < 0.05 p-values were calculated by Student's t-test, chi-squared test, Fisher's exact test or Mann–Whiney U test. Data were described as numbers of cases (%) for qualitative variables and as means (±SD) or medians (min-max) for quantitative variables.
Abbreviations: n: number, SD: standard deviation, y: years, COPD: Chronic obstructive pulmonary disease, CV: cardiovascular, CKD: chronic kidney disease, CVD: Cerebrovascular disease, APACHE II: acute physiology and chronic health evaluation-II scores, GCS: Glasgow Coma Scale, MV: mechanical ventilation, LOS: length of stay, ICU: intensive care unit.

The survivor and non-survivor groups were compared in terms of laboratory parameters. There was a significant difference between the two groups in terms of markers showing inflammation, including absolute lymphocyte and neutrophil count, CRP, procalcitonin, ferritin, and IL-6 measured on the day of ICU admission (p<0.05). The median absolute lymphocyte count of all patients hospitalized in the COVID-19 ICU was 0.83 (range, 0.53-3.32), with lymphocyte count being significantly lower in the non-survivor group (0.78 [range, 0.53-2.02]) compared to the survivor group (0.97 [range, 0.72-3.32]) (p<0.05) (**Table 2**). The cut-off value of lymphocyte for predicting mortality was 0.920 (AUC: 0.832 [95% CI 0.776-0.888]) (p<0.05). The median NLR of the entire population was 10.22 (range, 0.65-74.60); the median NLR of the non-survivor group (12.06 [range, 0.65-74.60]) was higher than that of the survivor group (7.21 [range, 0.97-37.69]) (p<0.05). The cut-off value of NLR for predicting mortality was 7.853 (AUC: 0.688 [95% CI 0.614-0.761]) (p<0.05).

The analysis of platelet count, MPV, PCT and PDW revealed no significant difference between the two groups. The comparison of the two groups in terms of platelet ratios showed higher PLR (321.79 [range, 51.16-1250.75] / 244.64 [range, 29.82-661.84]) and MPV/PLT ratio (0.035 [range, 0.010-0.230] / 0.030 [range, 0.010-0.130]) in the non-survivor group compared to the survivor group (p<0.05). The evaluation with ROC curve for predicting mortality revealed a cut-off value of 292.20 for PLR (AUC: 0.601 [95% CI 0.522-0.681]) (p<0.05) and a cut-off value of 0.0289 for MPV/PLT (AUC: 0.590 [95% CI 0.510-0.671]) (p<0.05) (**Figure 1**).



Variables	cutoff	Sensitivity	Specificity	AUC (%95 CI)	p
PLR	292,2068	0,575	0,670	0,601 (0,522-0,681)	**0,014**
MPV/PLT	0,0289	0,726	0,500	0,590 (0,510-0,671)	**0,028**
NLR	7,8537	0,752	0,534	0,688 (0,614-0,761)	**<0,001**

Figure 1. The Receiver Operating Characteristic (ROC) curve analysis for PLR, MPV/PLT, NLR for predicting ICU mortality
Abbreviations: ROC: Receiver Operating Characteristic, ICU: intensive care unit, AUC: area under the curve, CI: confidence interval, PLR: platelet-to-lymphocyte ratio, MPV/PLT: mean platelet volume-to-platelet count, NLR: neutrophil-to-lymphocyte ratio.

Table 2. Laboratory parameters of survivor and non-survivor patients

Variables	All Patients (n=201)	Survivors (n=88, 43.8%)	Non-survivors (n=113, 56.2%)	p
Hemoglobin (gr/dL)	12.50±2.14	12.55±2.15	12.47±2.15	0.783
WBC (×10^9/L)	10.49 (0.59-59.00)	9.63 (2.04-35.13)	11.20 (0.59-59.00)	0.156
Lymphocyte (×10^9/L)	0.83 (0.53-3.32)	0.97 (0.72-3.32)	0.78 (0.53-2.02)	<0.001*
Neutrophile (×10^9/L)	9.29 (0.44-54.46)	7.91 (1.76-30.53)	10.10 (0.44-54.46)	0.042*
Platelet (×10^9/L)	268 (38-838)	292 (81-662)	260 (38-838)	0.055
MPV (f/l)	8.9 (7.1-14.2)	8.7 (7.1-14.2)	9.0 (7.4-14.1)	0.083
PCT (%)	0.24 (0.05-0.74)	0.27 (0.08-0.60)	0.23 (0.05-0.74)	0.055
PDW (%)	55.70 (15.40-83.60)	55.25 (31.60-78.80)	57.00 (15.40 (83.60)	0.621
PLR	283.87 (29.82-1250.75)	244.64 (29.82-661.84)	321.79 (51.16-1250.75)	0.014*
NLR	10.22 (0.65-74.60)	7.21 (0.97-37.69)	12.06 (0.65-74.60)	<0.001*
MPV/PLT	0.034 (0.010-0.230)	0.030 (0.010-0.130)	0.035 (0.010-0.230)	0.028*
CRP (g/L)	0.100 (0.002-0.630)	0.081 (0.003-0.311)	0.131 (0.002-0.630)	<0.001*
Procalcitonin (µg/L)	0.18 (0.02-178.80)	0.12 (0.02-178.80)	0.23 (0.02-37.60)	<0.001*
Ferritin (µg/L)	713 (9-19000)	429 (14-19000)	815 (9-14273)	0.003*
IL-6 (pg/ml)	46.3 (4.7-1000.0)	31.9 (4.7-1000.0)	58.9 (5.0-1000.0)	<0.001*
AST (U/L)	49 (4-2900)	42 (4-382)	53 (12-2900)	0.006*
ALT (U/L)	37 (6-1605)	39 (6-383)	35 (7-1605)	0.996
D-dimer (mg/L)	2.0 (0.3-35.2)	1.45 (0.3-35.2)	2.2 (0.3-35.2)	0.018*

* Significant difference at $p < 0.05$. p-values were calculated by Student's t-test or Mann–Whiney U test. Data were described as means (±SD) or medians (min-max) for quantitative variables. **Abbreviations:** n: number, WBC: white blood cells, CRP: C-reactive protein, MPV: mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, PLR: Platelet-to-lymphocyte ratio, PLT: platelet, MPV/PLT: mean platelet volume-to-platelet count, NLR: neutrophil-to lymphocyte ratio, IL-6: Interleukin-6, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

DISCUSSION

Despite the decrease in the number of cases compared to two years ago, it cannot be anticipated when the pandemic will end. Since the beginning of the pandemic, the vast majority of patients with severe COVID-19 have been followed in ICUs. Especially in the periods when the number of cases peaked, the number of ICU beds was insufficient to meet the need, leading to high mortality rates worldwide. In critical cases, it is valuable to determine the risk factors at the time of admission and to have inexpensive, easily accessible parameters for predicting the prognosis in order to prevent negative outcomes. Although there are many studies on COVID-19 in the literature, a mortality marker that can be easily accessed and used in clinical practice to predict the prognosis of critically ill ICU patients with COVID-19 has not yet been defined.

Platelets are mainly responsible for hemostasis and are known to affect the immune system. Platelet count and platelet indices have been reported to be associated with inflammation and, effective in predicting the prognosis of patients with sepsis, with feasibility as a mortality marker in non-COVID-19 critically ill patients (8,11). Studies have shown higher mortality rates in patients with low platelet count among adult COVID-19 patients (12). However, although low platelet counts are associated with mortality in COVID-19 patients, thrombocytopenia is usually seen in very severe cases, with a low incidence of overt thrombocytopenia (13,14). In ICU patients, thrombocytopenia can have different causes, such as hemodilution, bacterial septicaemia, and bone marrow suppression (15). So, it would not be reasonable to use platelet counts alone as an indicator of mortality. Although the results of our study showed a lower platelet count in non-survivors compared to survivors, there was no statistically significant difference between the two groups. Therefore, the role of platelet indices in predicting mortality was evaluated in our study since these parameters have been reported to be more sensitive for predicting prognosis compared to platelet count in non-COVID-19 critically ill patients but have not been studied in large series to demonstrate the mortality relationship in ICU patients with COVID-19.

In the literature, there are various studies examining platelet indices in different patient groups with non-critical COVID-19. A paper comparing COVID-19 outpatients with non-COVID-19 patients reported higher MPV and PDW and lower PCT in the COVID-19 group than in the control group, suggesting that these parameters may be a warning for the suspicion of COVID-19 at the diagnosis stage (16). Guclu et al. (9) compared moderate and severe COVID-19 cases found no difference between the survivor and non-survivor groups in terms of admission MPV values and reported an association with a 1.76-fold increase in mortality for every 1 unit increase in the follow-up MPV measured on day 3. Our study evaluating ICU patients with COVID-19 showed no difference in MPV, PCT, and PDW parameters evaluated at ICU admission. PLR and MPV/PLT ratio were higher in the non-survivor group and were associated with mortality. Studies suggest the use of MPV/PLT and PLR as a prognostic indicator instead

of MPV or platelet indices alone in non-COVID-19 ICU patients (17). A small-series study evaluating the admission parameters of 96 ICU patients in the COVID-19 patient group found no difference between non-survivors and survivors in terms of the admission MPV value but reported the significance of the MPV/PLT ratio in demonstrating mortality (18). The study of Yardimci et al. (19) evaluating 722 patients hospitalized in COVID-19 wards reported that 44 patients were transferred to ICU and the MPV/PLT ratio of severely ill patients who required ICU were higher compared to those treated in wards. However, the study did not mention the relationship between MPV/PLT ratio and mortality. We believe that our study, which demonstrated a significant difference in MPV/PLT ratios between the non-survivor and survivor groups, will come to the fore both because it included patient population consisting entirely of ICU patients and it primarily evaluated ICU mortality.

PLR, which is associated with systemic inflammation, is a parameter that has been used as a new generation inflammation marker in recent studies in various infection case groups such as septicemia and pneumonia. The study of Shen et al. (20) on non-COVID-19 critically ill patients evaluating 5537 ICU patients with sepsis reported a strong association between PLR >200 and mortality. A COVID-19 study evaluating 306 patients reported higher PLR in patients who developed pneumonia compared to those who did not, stating that a PLR cut-off value of 139 could be used for predicting the development of pneumonia (21). A review evaluating PLR in COVID-19 cases explained the more significant association of high admission PLR with mortality compared to other platelet parameters by the increase in PLR as a result of deeper lymphopenia compared to thrombocytopenia in baseline examinations (22). It is known that a cytokine storm can develop in ICU patients with COVID-19, leading to high mortality rates. Evaluation of PLR, as a systemic inflammation indicator, at the time of ICU admission may be a guide in identifying the progression to septicemia or cytokine storm in this patient group, thus preventing mortality. In our study, PLR was higher in the non-survivor group, and the cut-off value of PLR for predicting mortality was found to be 292.20.

COVID-19 infection causes an increase in infection parameters due to rapid viral replication and the uncontrolled release of pro-inflammatory cytokines and chemokines. Numerous studies have been conducted with inflammation markers to evaluate the prognosis and mortality of COVID-19 patients during the pandemic (23). There are studies evaluating leukocyte subsets and pro-inflammatory cytokine levels such as IL-6, IL-1, IL-10, and TNF in COVID-19 which is known to cause hyper-inflammation and cytokine storm (24). However, the parameters to predict the prognosis in epidemic situations that affect the whole world and cause pandemics should be cost-effective tests that can be performed anywhere. CBC is an inexpensive and easily accessible test. Lymphopenia is known to be common in viral infections. Therefore, one of the parameters frequently investigated in patients with COVID-19 has been the lymphocyte count. A study by Wang et al. (7) reported that a lymphocyte count of less than 0.95 × 109/L was associated with higher mortality compared to a lymphocyte count of > 0.95 × 109/L. The ROC analysis performed in our study revealed a cut-off value of 0.920 × 109/L for the lymphocyte count to predict mortality.

NLR is another CBC parameter reported to be associated with the severity of COVID-19. As a result of studies conducted with non-COVID-19 patients in the literature, it is known that NLR shows mortality more sensitively than isolated neutrophil and lymphocyte levels in viral and bacterial pneumonia (25). A retrospective study of 151 COVID-19 patients reported a median NLR value of 1.95 (1.43–2.58) in survivors and 13.87 (7.50–24.82) in non-survivors. However, the study did not indicate the number of patients who required ICU (26). In our study, the cut-off of NLR value for predicting mortality was 7.85. The results of our study evaluating critically ill patients with COVID-19 showed significantly higher median NLR in the non-survivor group compared to the survivor group. It is believed that this rate increases with the severity of the disease. A meta-analysis of 38 articles evaluating admission NLR levels of patients with COVID-19 reported higher NLR in severe COVID-19 cases and in the non-survivor group (27). These studies evaluating CBC parameters in COVID-19 generally include the outpatient groups, while our study, the entire population of which consisted of ICU patients with COVID-19, differs from the published studies in the literature in this regard. The limitation of our study is its retrospective and single-center design. We believe that prospective multicenter studies will support these results.

CONCLUSION

The results of our study evaluating platelet indices for predicting mortality of ICU patients during the pandemic demonstrated an association between PLR, MPV/PLT ratio, and mortality. Using ratios such as MPV/PLT and PLR as an early prognostic indicator instead of platelet indices alone, like MPV in ICU patients with COVID-19, may help identify high-risk patients early. We believe that our study will shed light on future studies in terms of using these easily accessible and cost-effective CBC parameters in clinical practice to identify high-risk patients early at the time of admission and prevent poor outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee (Approval Number: 2021/E2-21-358 and Approval Date: 07.04.2021) for studies involving humans.

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. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https //covid19.who.int/ (accessed date: 19 April 2022).
2. Marin BG, Aghagoli G, Lavine K, et al. Predictors of COVID-19 severity: A literature review. Rev Med Virol 2021; 31:1-10.
3. Qi J, He D, Yang D, et al. Severity-associated markers and assessment model for predicting the severity of COVID-19: a retrospective study in Hangzhou, China. BMC Infect Dis 2021; 21: 774.
4. Hou H, Zhang B, Huang H, et al. Using IL-2R/lymphocytes for predicting the clinical progression of patients with COVID-19. Clin Exp Immunol 2020; 201: 76-84.
5. Smilowitz NR, Kunichoff D, Garshick M, et al. C-reactive protein and clinical outcomes in patients with COVID-19. Eur Heart J 2021; 42: 2270-9.
6. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020; 58: 1021-8.
7. Wang S, Sheng Y, Tu J, Zhang L. Association between peripheral lymphocyte count and the mortality risk of COVID-19 inpatients. BMC Pulm Med 2021; 21: 55.
8. Vardon-Bounes F, Gratacap MP, Groyer S, et al. Kinetics of mean platelet volume predicts mortality in patients with septic shock. PLoS One 2019; 14: e0223553.
9. 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.
10. Vélez-Páez JL, Legua P, Vélez-Páez P, et al. Mean platelet volume and mean platelet volume to platelet count ratio as predictors of severity and mortality in sepsis. PLoS One 2022; 17: e0262356.
11. Zhang Z, Xu X, Ni H, Deng H. Platelet indices are novel predictors of hospital mortality in intensive care unit patients. J Crit Care 2014; 29: 885.
12. Liu Y, Sun W, Guo Y, et al. Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. Platelets 2020; 31: 490-6.
13. Larsen JB, Pasalic L, Hvas AM. Platelets in coronavirus disease 2019. Semin Thromb Hemost 2020; 46: 823-5.
14. Pujani M, Raychaudhuri S, Verma N, et al. Association of Hematologic biomarkers and their combinations with disease severity and mortality in COVID-19- an Indian perspective. Am J Blood Res 2021; 11: 180-90.
15. Ostadi Z, Shadvar K, Sanaie S, Mahmoodpoor A, Saghaleini SH: Thrombocytopenia in the intensive care unit. Pak J Med Sci 2019; 35: 282-7.
16. Shankaralingappa A, Tummidi S, Arun Babu T. Diagnostic value of platelet indices in COVID 19 infection: a case-control study from a single tertiary care center. Egypt J Intern Med 2022; 34: 35.
17. Golwala ZM, Shah H, Gupta N, Sreenivas V, Puliyel JM. Mean platelet volume (MPV), platelet distribution width (PDW), platelet count and plateletcrit (PCT) as predictors of in-hospital paediatric mortality: a case-control Study. Afr Health Sci 2016; 16: 356-62.
18. Mobarki AA, Dobie G, Saboor M, et al. MPR and NLR as prognostic markers in ICU-admitted patients with COVID-19 in Jazan, Saudi Arabia. Infect Drug Resist 2021; 14: 4859-64.
19. Yardımcı AC, Yıldız S, Ergen E, et al. Association between platelet indices and the severity of the disease and mortality in patients with COVID-19. Eur Rev Med Pharmacol Sci 2021; 25: 6731-40.
20. Shen Y, Huang X, Zhang W. Platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity-a retrospective study. BMJ Open 2019; 9: e022896.
21. Damar Çakırca T, Torun A, Çakırca G, Portakal RD. Role of NLR, PLR, ELR and CLR in differentiating COVID-19 patients with and without pneumonia. Int J Clin Pract 2021; 75: e14781.
22. Sarkar S, Kannan S, Khanna P, Singh AK. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: a systematic review and meta-analysis. J Med Virol 2022; 94: 211-21.
23. Gao YD, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: a review. Allergy 2021; 76: 428-55.
24. Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol 2020; 108: 17-41.
25. Han Q, Wen X, Wang L, et al. Role of hematological parameters in the diagnosis of influenza virus infection in patients with respiratory tract infection symptoms. J Clin Lab Anal 2020; 34: e23191.
26. Wang X, Li X, Shang Y, et al. Ratios of neutrophil-to-lymphocyte and platelet-to-lymphocyte predict all-cause mortality in inpatients with coronavirus disease 2019 (COVID-19): a retrospective cohort study in a single medical centre. Epidemiol Infect 2020; 148: e211.
27. Simadibrata DM, Calvin J, Wijaya AD, Ibrahim NAA. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis. Am J Emerg Med 2021; 42: 60-9.

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The prognostic value of androgenetic alopecia and benign prostatic hyperplasia in men with COVID-19: a prospective multidisciplinaryobservational study of 766 patients from Turkey

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ABSTRACT

Objectives: We aimed to investigate the prognostic value of androgenetic alopecia (AGA) and benign prostatic hyperplasia (BPH) in COVID-19.

Material and Method: This prospective study was conducted only on men with COVID-19. All patients were recruited consecutively from the COVID-19 emergency service. 766 patients were evaluated in three independent groups between the ages of 30-49 (young), 50-64 (middle-aged), and 65-75 (elderly) to avoid Simson's paradox. Age, body mass index, smoking, comorbidities, vital signs, oxygen saturation (SpO_2%), laboratory (CRP, lymphocyte count, ferritin, d-dimer) and computed tomography (CT) results, hospitalization (primary endpoint), transfer to intensive care unit (ICU), AGA stage (Hamilton-Norwood scale, 3-7=moderate-severe AGA, Gabrin sign) and BPH were recorded.

Results: There was no relationship with AGA in any prognostic parameter in the young age group. There was a significant difference in the poor prognostic direction in patients with Gabrin sign, in SpO_2 and lymphocyte count for middle-aged, and CRP for the elderly (p=0.141, p=0.013, p=0.029; respectively). The frequencies of transfer to the ICU were higher with no statistical significance in patients with the Gabrin sign. The mortality was more common with no statistical significance in elderly patients with the Gabrin sign. Hospitalization frequencies were significantly higher in patients with BPH in middle-aged and elderly patients (p=0.041, p=0.026; respectively). No relationship was found between transfer to ICU, mortality, and BPH.

Conclusions: AGA was not a prognostic indicator, though the increase in hospitalization frequency, particularly in elderly patients with BPH, may be associated with the androgen-mediated COVID-19 severity hypothesis.

Keywords: Androgenetic alopecia, Gabrin sign, benign prostatic hypertrophy, COVID-19, prognosis, hospitalization

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic was declared by the World Health Organization on March 11, 2020 (1). During the pandemic, it has been reported that severe course and death from COVID-19 are more common in adulthood than pre-pubertal period (1). Prognosis is significantly worse in men independent of age, though the incidence of COVID-19 is similar across genders (2). Although reasons such as smoking, lifestyle habits, and anatomical and immunological differences are reasonable to explain male dominance in COVID-19 infection and mortality, they cannot explain the significantly reduced risk in pre-puberty children (3).

The presence of concomitant androgenetic alopecia (AGA) in patients indicates cumulative androgen exposure over decades. Wambier and Goren reported that the course of COVID-19 might be androgen-related, based on some epigenetic and epidemiological data (4).

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Wambier et al. (5) claimed that particularly severe AGA in young men, which means the Hamilton-Norwood scale (HNS)=3-7, causes increased sensitivity to COVID-19.

The androgen pathway in COVID-19 infection is as in **Figure 1**. It has been shown in animal experiments that dihydrotestosterone inhibits fetal pulmonary surfactant production in both men and women, while flutamide, an anti-androgen, increases it (6). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly infects type II pneumocytes in the human lung. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) cell surface receptor and enters pneumocytes. However, before that, spike proteins and ACE2 need to be prepared for viral spread and pathogenesis by transmembrane protease, serine 2 (TMPRSS2) (7). Androgen is the only known TMPRSS2 gene promoter in humans (8). TMPRSS2 was shown to be more expressed in normal lung tissue in men than in women (9). The disproportionate mortality rate observed in patients with COVID-19 in African-Americans was thought to be related to the polymorphisms of the androgen receptor leading to increased androgen sensitivity reported in this ethnic group (10-12). Montopoli et al. (13) compared the outcomes of COVID-19 in patients with prostate cancer according to whether they received anti-androgen therapy or not. They reported that the risk of COVID-19 was approximately 4-times higher in prostate cancer patients who did not receive anti-androgen therapy. However, some contradictory data should not be overlooked. It is known that mortality increase with age, although testosterone level decreases in elderly men. Recent studies have emphasized that disease activity is related to some specific gene loci rather than ACE2 or TMPRSS2 (14). Serum androgen level is not always correlated with tissue androgen or its effect (15). Interestingly, it is highlighted that ACE2 expression can be enhanced by androgen suppression, unlike decreased TMPRSS2 expression (16). Therefore, ACE2 expression can be enhanced by androgen suppression. Whether this will result in an apparent increase in the risk of severe infection is unknown due to the complex nature of the endocrine system and pathways.

In light of these data, it can be suggested that androgen-related diseases such as AGA, benign prostatic hyperplasia (BPH), prostate cancer, and PCOS may be associated with the severity of pneumonia, hospitalization, and prognosis. However, epidemiological evidence is still inadequate and conflicting. We aimed to investigate whether it was associated with the AGA stage and the presence of BPH. The primary endpoint of this study was the frequency of hospitalization. Secondary, we investigated the relationship between computed tomography (CT) results and various prognostic parameters with AGA and BPH in male patients with COVID-19.

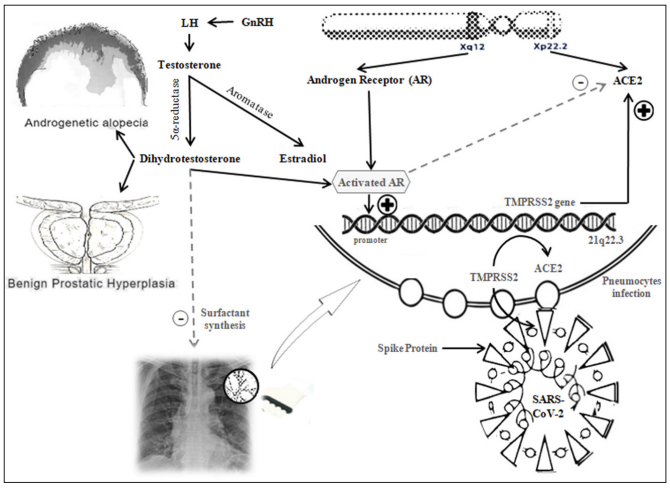

Figure 1. Androgen pathway in COVID-19 infection.

GnRH: Gonadotropin-releasing hormone, LH: Luteinizing hormone, TMPRSS2: Transmembrane protease, serine 2, ACE2: Angiotensin-converting enzyme 2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

MATERIAL AND METHOD

This single-center, prospective, multidisciplinary, observational, cross-sectional study was approved by the local ethics committee (Date: 19.10.2020, Decision No: 2020/19-185) and the Scientific Research Platform of the Ministry of Health (2020-09-18T11_21_01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent forms were obtained from all patients.

This study was conducted only on male patients with confirmed COVID-19 (symptomatic or asymptomatic). All patients were recruited consecutively from the COVID-19 emergency service (positive stable patient zone and yellow zones) in the Erzurum Regional Training and Research Hospital, the only pandemic hospital in the province, between 01 September- 15 December 2020. The task distribution scheme for applications to the COVID-19 emergency department in the pandemic hospital is described in **Figure S1**. Medically, all patients were approached in line with the Republic of Turkey, Ministry of Health's COVID-19 guidelines (17). The patient's age, body mass index (BMI), current smoking, comorbidities, current medications, vital signs, oxygen saturation measured with a pulse oximeter (SpO_2), and laboratory results are recorded in the study protocol form. In the presence of an appearance compatible with COVID-19 pneumonia[CT (+)], the severity (<50% mild-moderate, >50% severe) according to the area of radiological involvement was noted.

In the presence of pneumonia, the predicted pneumonia prognosis was also evaluated with the CURB-65 scale (confusion, urea>42.8 mg/dl, respiratory rate>30/min, blood pressure-systolic<90 mm/Hg or diastolic<60 mm/Hg, age>65) at admission. Also, considering that using prognostic biomarkers as a scale variable in our study may lead to reaching statistical significance that does not

indicate clinical significance, we determined the cut-off values according to guidelines published by the coronavirus Scientific Board of Turkey: blood lymphocyte count <800/µl or CRP >40 mg/dl or ferritin >500 ng/ml or d-dimer >1000 ng/ml.17 After the study was terminated, all patients' files were scanned in the hospital, public health database, and their disease processes were evaluated in terms of laboratory and CT results, prognosis, hospitalization, and length of stay in the hospital (LOS), transfer to the intensive care unit (ICU), and mortality. Thus, we based on the highest/worst records in parameters such as SpO_2, poor prognostic indicators, and CT in outpatients and inpatients during the disease process. The patient's medical history and current medications were confirmed on the social security institution website, and false entries have been corrected(https://medeczane.sgk.gov.tr/doktor/login.jsp).

AGA stage was recorded between 1 and 7, according to HNS. The scores were categorized into two groups: ''no or mild AGA" for HNS≤2 and "moderate and severe AGA" for HNS=3-7 indicating the Gabrin sign. Patients were questioned in terms of the presence of lower urinary tract symptoms (LUTS) associated with BPH, history of BPH, and their medical treatments for BPH. International prostate symptom score (IPSS) was also evaluated. The prostate-specific antigen values and uroflowmetry results of patients in the last 1 year were screened retrospectively. Patients who were considered to have BPH with all these documents by the urologist were included in the study. LUTS can develop secondary to urethral stricture (18). Thus patients with a history of urethral stricture or bladder stones and prostate cancer were excluded.

The study design used was a retrospective cohort. Data were obtained from the medical and financial records of SCH. and QoL. Decision tree analysis was performed in this study with financing and clinical outcomes as parameters. The inclusion criteria were as follows men above 50 years who were diagnosed with BPH by a urologist, and currently taking Tamsulosin (0.4 mg) and Dutasteride (0.5 mg). We excluded patients with prostate cancer or other diseases that can cause LUTS except for BPH. All patients who refused and didn't complete the routine follow-up were also excluded. Then we divided the patients into standard therapy method group (Group 1) and modified therapy method (Group 2). Clinical outcomes and costs were then analyzed between the two groups.

Inclusion criteria in the study were being a Caucasian male between the ages of 30-75 and giving informed consent. Probable COVID-19 [PCR (-), CT (+)] patients were excluded.Diseases such as morbid obesity, rheumatological diseases, chronic respiratory diseases (moderate-severe COPD/Asthma, and pulmonary hypertension), heart failure, malignant arrhythmia, chronic renal failure (estimated glomerular filtration rate≤60 ml/min), immune deficiencies, and cancers were excluded, except for diabetes mellitus, hypertension, and coronary artery disease, provided that they are under control with treatment.

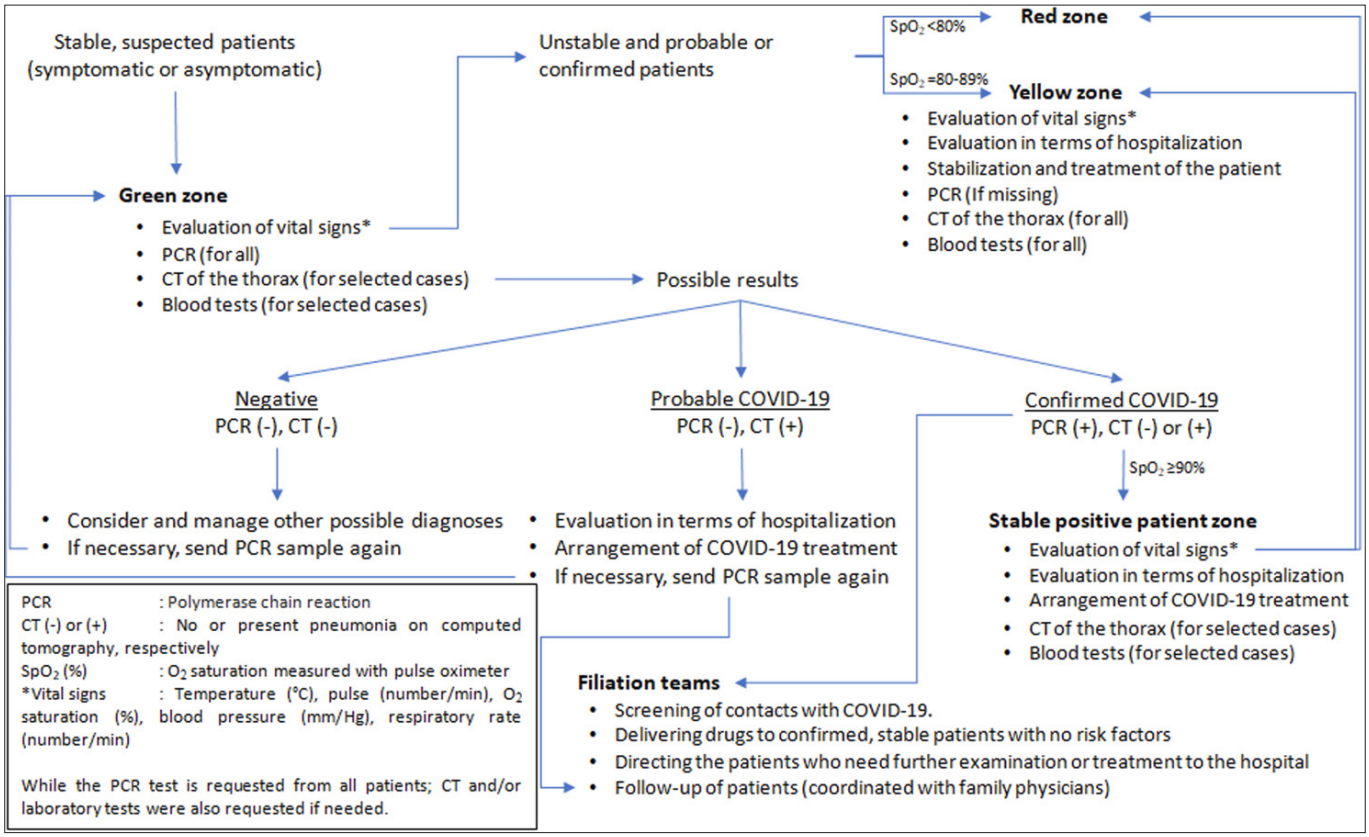

Figure S1. The task distribution scheme for applications to the COVID-19 emergency department in the pandemic hospital

Patients using oral or inhaled steroids, any antiandrogenic drugs, and transmembrane protease-serine 2 (TMPRSS2) blockers (bromhexine, camostat, and naphamostat) were not included in the study.

Simson's paradox expresses the discrepancy between conditional and marginal interpretations of the data (19). The sample was divided into three different age groups to avoid Simson's paradox, as age is a crucial prognostic factor in COVID-19 and the frequency and severity of comorbidities such as AGA and BPH increase with age. All statistical procedures were conducted using SPSS Statistics 21.0, G*Power 3.1, and MS-Excel 2010. Results were presented as the median (interquartile range) ormean±standard deviation or number of patients (percentage). Pearson chi-square and Fisher's exact test were used for categorical variables, where appropriate. After checking the normality distribution of scale variables by Kolmogorov-Smirnov, independent samples were compared with the Mann-Whitney-U test. Priori and post-hoc power analyses were performed for each parameter individually for two-sided α=0.05, power (1- β)=0.80 at a confidence level of 95% (20). Effect sizes were obtained for scale variables by transforming the Eta squared (η2), which was obtained using the Z-values, into Cohen's d (21,22). Cramer's V (φc) was used for categorical variables.

RESULTS

With age, the increasing mortality rate of COVID-19 and the marked change in the frequency and stage of AGA and BPH made it an important confounder for this study. Therefore, 766 patients who participated in our study were evaluated separately in three independent groups between the ages of 30-49 (young patients, n=309), 50-64 (middle-aged patients, n=262), and 65-75 (elderly patients, n=195), respectively to adjust the age factor in the prognosis of COVID-19 and adjust the age with the AGA stage and BPH. As seen in **Table 1**, confounding factors in terms of prognosis such as age, comorbidities, and current smoking in patients with and without Gabrin sign or BPH were statistically similar in all groups except for only two parameters. The frequencies of current smoking in young patients without severe AGA and hypertension in elderly patients with BPH were significantly higher (p<0.001, p=0.024, respectively). The mean age of all patients was 52.3±13.2 years. The central tendency and distribution measurements of age belonging to the five groups for AGA and BPH were presented in **Table 1**. The distribution of Gabrin sign and BPH in various prognostic groups by age in COVID-19 patients is presented in **Figure 2**.

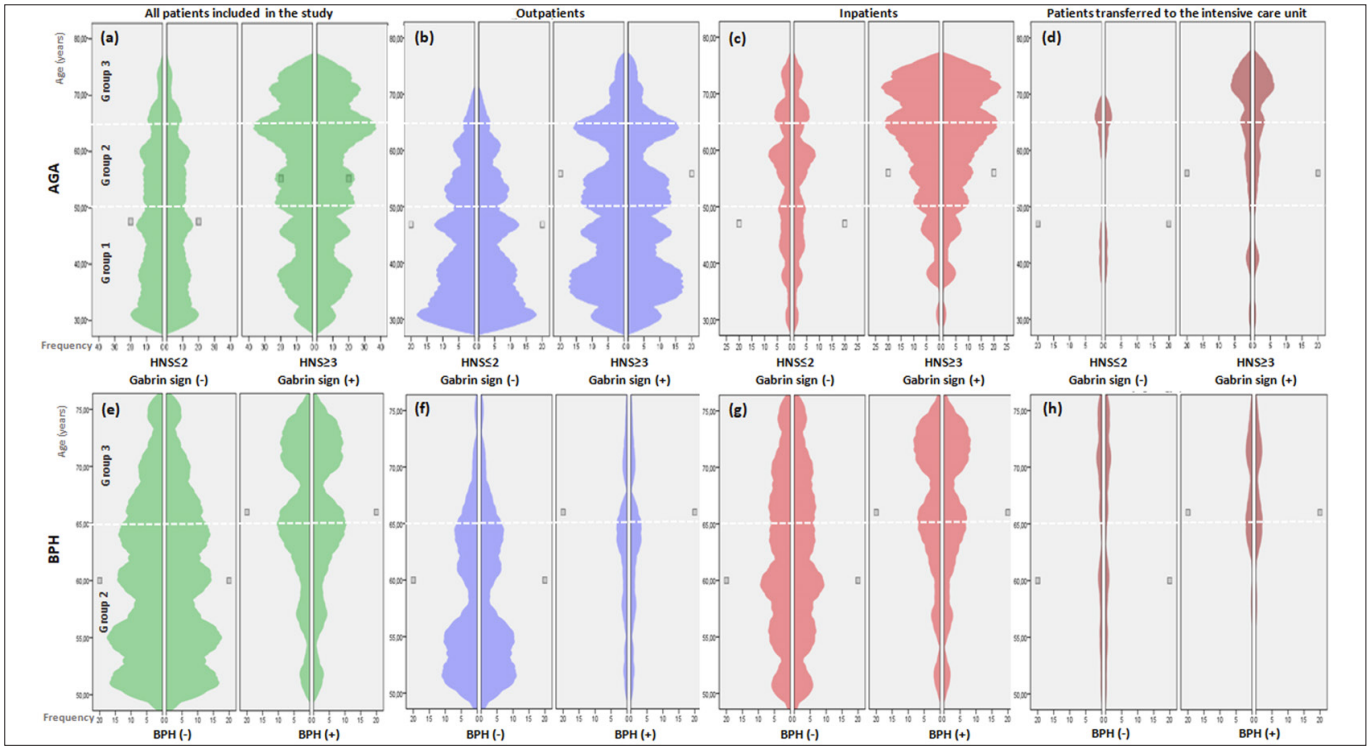

Figure 2. Distribution of Gabrin sign and BPH in various prognostic groups in COVID-19 patients by age: Violin plot

Androgenetic alopecia (AGA) severity was categorized by Hamilton-Norwood scale (HNS) for men into groups: "no alopecia and mild alopecia" for HNS=1-2; "moderate-severe AGA" for HNS=3-7 (Gabrin sign). Wider sections of the violin plot represent a higher probability that members of the population will take on the given value; the skinnier sections represent a lower probability. A possible significant change in the distribution trend can be predicted when each graph is compared with its partner at the same level and the general population (all patients).

The top row: Age and Gabrin sign appear to be closely related. The violin plot suggests that the distribution of Gabrin signs by age differs according to the general population (a) in the outpatient (b) and inpatients (c). It is curious whether this difference is due to the more frequent hospitalization of elderly patients or the possible prognostic value of the Gabrin sign.

The lower row: Comparing outpatients (f) and inpatients (g), it is understood that relatively few of the COVID-19 patients with benign prostatic hypertrophy (BPH) were followed-up at home as outpatients.

Table 1. Confounding factors possibly associated with COVID-19 prognosis

Confounders	Androgenic alopecia			Benign prostate hyperplasia		
	HNS=1-2 Gabrin sign (-)	HNS=3-7 Gabrin sign (+)	p-value	No	Yes	p-value
Group 1 (age of 30-49) Young patients						
Number (row %) of patients	150 (48.5%)	159 (51.5%)	-	-	-	-
Age (years)-median (IQR)	38 (11)	39 (10)	0.074*			
Diabetes mellitus	9 (6.0%)	8 (5.1%)	0.709			
Hypertension	7 (4.7%)	9 (5.7%)	0.694			
Coronary artery disease	1 (0.7%)	1 (0.6%)	1.000**			
Benign prostate hyperplasia	0 (0.0%)	1 (0.0%)	1.000**			
Other diseases †	11 (7.3%)	9 (5.7%)	0.550			
ACEi or ARB	0 (0.0%)	3 (1.9%)	0.248**			
Current smoking	58 (38.9%)	32 (20.1%)	<0.001			
BMI (kg/m²)-median (IQR)	26.9 (3.6)	27.4 (4.4)	0.065*			
Group 2 (age of 50-64) Middle-aged patients						
Number (row %) of patients	86 (32.8%)	176 (67.2%)	-	205 (78.2)	57 (21.8%)	-
Age (years)-median (IQR)	57 (7)	57 (8)	0.128*	58 (7)	59 (7)	0.099*
Diabetes mellitus	16 (18.6%)	44 (25.1%)	0.238	44 (21.6%)	16 (28.1%)	0.302
Hypertension	24 (27.9%)	57 (32.4%)	0.461	60 (29.4%)	21 (36.8%)	0.284
Coronary artery disease	4 (4.7%)	10 (5.7%)	1.000**	11 (5.4%)	3 (5.3%)	0.914**
Benign prostate hyperplasia	17 (19.8%)	40 (22.9%)	0.570	-	-	
Other diseases ‡	12 (14.0%)	20 (11.4%)	0.548	25 (12.3%)	7 (12.3%)	0.996
ACEi or ARB	12 (14.0%)	31 (17.6%)	0.453	33 (16.2%)	10 (17.5%)	0.806
Current smoking	23 (27.7%)	30 (17.2%)	0.052	37 (18.4%)	16 (29.1%)	0.083
BMI (kg/m²)-median (IQR)	27.3 (4.2)	28.3 (5.3)	0.056*	27.9 (5.3)	28.4 (4.6)	0.853*
Group 3 (age of 65-75) Elderly patients						
Number (row %) of patients	30 (15.4%)	165 (84.6%)	-	82 (50.0%)	82 (50.0%)	-
Age (years)-median (IQR)	68 (7)	69 (8)	0.161*	68.5 (5)	70 (7)	0.115*
Diabetes mellitus	10 (33.3%)	55 (33.3%)	1.000	27 (32.9%)	30 (36.6%)	0.623
Hypertension	16 (53.3%)	105 (63.6%)	0.285	44 (53.7%)	58 (70.7%)	0.024
Coronary artery disease	8 (26.7%)	39 (23.6%)	0.721	28 (34.1%)	19 (23.2%)	0.120
Benign prostate hyperplasia	10 (35.7%)	72 (57.6%)	0.097	-	-	-
Other diseases §	18 (60.0%)	93 (57.0%)	0.757	40 (48.8%)	41 (50.2%)	0.876
ACEi or ARB	13 (43.3%)	55 (33.3%)	0.290	27 (32.9%)	29 (35.4%)	0.742
Current smoking	9 (30.0%)	26 (15.8%)	0.062	14 (17.1%)	16 (19.5%)	0.686
BMI (kg/m²)-median (IQR)	27.8 (3.8)	27.0 (5.8)	0.832*	26.2 (6.3)	27.5 (5.4)	0.055*

HNS: Hamilton-Norwood scale, IQR: Inter-quartile range, ACEi: Angiotensin-converting-enzyme inhibitors, ARB: Angiotensin II Receptor Blockers, BMI: Body mass index, † Other diseases in young patients: Dyslipidemia, gastritis/reflux, anxiety disorder, thyroid diseases, migraine, urticaria, brucella, chronic hepatitis B, asthma / allergic rhinitis, arrhythmias, ‡ Other diseases in middle-aged patients: Gastritis/reflux, dyslipidemia, thyroid diseases, musculoskeletal diseases, depression, sleep disorder, urticaria, arrhythmias, vitamin D-B12 deficiency, § Other diseases in elderly patients: Gastritis, thyroid diseases, dyslipidemia, musculoskeletal diseases, glaucoma, vitamin D-B12 deficiency, arrhythmias, sleep disturbance, depression, Parkinson's disease, The Mann–Whitney U test* and Pearson's chi-square or Fisher's exact tests** were used. Results were presented as the median (interquartile range) or number of patients (column percentage). Significant values were shown in bold.

The relationship between the AGA stage and BPH in different age groups with hospitalization, CT results, and various prognostic indicators in COVID-19 was presented in **Table 2** and **Table 3**, respectively. When **Table 2** was examined from a broad perspective, statistically no significant results were obtained in most parameters, including hospitalization. Also, effect sizes were small and even very small in almost all parameters when interpreted according to Cohen's tables. In the middle-aged patients, the frequency of $SpO_2 \leq 93\%$ was significantly higher in patients with Gabrin sign (all patients: φc=0.141, p=0.023; inpatients: φc=0.220, p=0.012). Hospitalization frequencies in the three groups had no differences according to the Gabrin sign (p=0.645, p:0.136, p:0.736; Group 1 to 3, respectively). A significant increase in the middle-aged and elderly inpatient groups was found in CRP values with small-medium effect sizes in those with Gabrin sign (d=0.382, p=0.047; d=0.405, p=0.044; respectively). However, CRP>40 mg/dl as a poor prognostic criterion was statistically more common in only elderly patients with Gabrin sign (all patients: φc=0.156, p=0.029, inpatients: φc=0.252, p=0.010). No relationship was found between LOS and AGA in any group (p=0.726, p=0.291, p=0.629; respectively). Although the frequencies of transfer to ICU were higher in patients with Gabrin sign in all groups, there was no statistically significant relationship between them with very small effect sizes (φc=0.066, p=0.715; φc=0.097, p=0.347; φc=0.071, p=0.380; respectively). Mortal outcomes were recorded, especially in the elderly patient group. Although the frequency of mortality in this group was more common in patients with severe AGA, there was no statistical significance with a very small effect size (φc=0.060, p=0.742).

Table 2. Relationship of AGA in different age groups with CT results and various prognostic indicators in COVID-19 cases

Parameters	Group 1 (age of 30-49 years)				Group 2 (age of 50-64 years)				Group 3 (age of 65-75 years)			
	HNS≤2	HNS≥3	Effect size	p value	HNS≤2	HNS≥3	Effect size	p value	HNS≤2	HNS≥3	Effect size	p value
CT severity in all confirmed follow-up cases †			0.078	0.463			0.103	0.279			0.040	0.861
No pneumonia	41 (34.5%)	37 (27.8%)			15 (19.2%)	26 (16.1%)			3 (10.0%)	12 (7.5%)		
Mild-moderate pneumonia	61 (51.3%)	78 (58.6%)			49 (62.8%)	91 (56.5%)			14 (46.7%)	73 (45.3%)		
Severe pneumonia	17 (14.3%)	18 (13.5%)			14 (17.9%)	44 (27.3%)			13 (43.3%)	76 (47.2%)		
Various prognostic indicators in all confirmed follow-up cases												
Asymptomatic =Yes	7 (4.7%)	9 (5.8%)	0.025	0.665	4 (4.7%)	8 (4.5%)	0.002	1.000**	1 (3.3%)	7 (4.3%)	0.017	1.000**
SpO_2 (%)	94.8±2.9	94.7±2.8	0.053	0.636*	93.0±3.6	91.9±4.6	0.250	0.043*	89.3±5.6	88.3±7.0	0.067	0.639*
SpO_2≤93%	27 (18.0%)	38 (23.9%)	0.072	0.203	36 (41.9%)	100 (56.8%)	0.141	0.023	24 (80.0%)	124 (75.2%)	0.041	0.568
SpO_2<90%	7 (4.7%)	5 (3.1%)	0.039	0.489	9 (10.5%)	30 (17.0%)	0.087	0.160	14 (46.7%)	75 (45.5%)	0.009	0.902
Pneumonia =Yes	78 (52.0%)	96 (60.4%)	0.084	0.138	63 (73.3%)	136 (77.3%)	0.044	0.475	27 (90.0%)	150 (90.9%)	0.011	0.744**
CT = Severe pneumonia ‡	17 (21.8%)	18 (18.8%)	0.038	0.618	14 (22.2%)	44 (32.6%)	0.106	0.135	13 (48.1%)	76 (51.0%)	0.021	0.785
C-reactive protein (mg/dl)	22.3±40.5	21.8±37.6	0.045	0.690*	45.5±72.7	59.1±67.1	0.198	0.110*	63.6±58.9	98.0±94.9	0.201	0.163*
C-reactive protein >40 mg/dl	19 (12.7%)	24 (15.1%)	0.035	0.538	28 (32.6%)	72 (40.9%)	0.081	0.191	11 (36.7%)	96 (58.2%)	0.156	0.029
Lymphocyte count<800/μl	13 (8.7%)	15 (9.4%)	0.013	0.814	14 (16.3%)	54 (30.7%)	0.154	0.013	16 (53.3%)	95 (57.6%)	0.031	0.666
Ferritin>500 ng/ml	30 (20.0%)	29 (18.2%)	0.022	0.694	22 (25.9%)	64 (36.4%)	0.104	0.091	15 (50.0%)	84 (51.2%)	0.009	0.902
d-dimer >1000 ng/ml	14 (9.4%)	20 (12.6%)	0.051	0.373	19 (22.4%)	41 (23.3%)	0.010	0.865	16 (53.3%)	99 (60.0%)	0.049	0.495
Hospitalization =Yes	28 (18.7%)	33 (20.8%)	0.026	0.645	37 (43.0%)	93 (52.8%)	0.092	0.136	23 (76.7%)	131 (79.4%)	0.024	0.736
Various prognostic indicators in only confirmed inpatients												
CURB-65 score at admission	0.3±0.5	0.3±0.5	0.035	0.858	0.6±0.6	0.7±0.7	0.143	0.367	2.1±0.6	2.2±0.8	0.039	0.781
SpO_2 (%)	90.9±4.3	92.4±4.5	0.393	0.129*	91.2±4.5	89.9±5.3	0.262	0.136*	88.2±5.8	86.7±7.0	0.143	0.374*
SpO_2≤93%	19 (67.9%)	18 (54.5%)	0.136	0.289	22 (59.5%)	75 (80.6%)	0.220	0.012	20 (87.0%)	114 (87.0%)	0.001	1.000**
SpO_2<90%	7 (25.0%)	5 (15.2%)	0.123	0.335	9 (24.3%)	28 (30.1%)	0.058	0.510	13 (56.5%)	74 (56.5%)	<0.001	0.996
CT = Severe pneumonia ‡	13 (48.1%)	15 (48.4%)	0.002	0.986	12 (34.3%)	36 (42.4%)	0.075	0.412	13 (59.1%)	74 (59.2%)	0.001	0.992
C-reactive protein (mg/dl)	77.7±58.6	70.1±56.1	0.115	0.623*	64.5±46.8	96.4±71.5	0.382	0.047*	62.0±51.5	115.4±98.5	0.405	0.044*
C-reactive protein >40 mg/dl	16 (57.1%)	19 (57.6%)	0.004	0.973	23 (62.2%)	62 (66.7%)	0.043	0.626	8 (35.0%)	92 (70.2%)	0.252	0.010
Lymphocyte count<800/μl	12 (42.9%)	13 (39.4%)	0.035	0.784	14 (37.8%)	47 (50.5%)	0.115	0.190	15 (65.2%)	90 (68.7%)	0.027	0.741
Ferritin>500 ng/ml	22 (78.6%)	21 (63.6%)	0.163	0.202	18 (50.0%)	55 (59.1%)	0.083	0.348	12 (52.2%)	83 (63.4%)	0.082	0.309
d-dimer >1000 ng/ml	10 (35.7%)	15 (45.5%)	0.099	0.441	14 (37.8%)	35 (37.6%)	0.002	0.983	16 (69.6%)	93 (71.0%)	0.011	0.890
LOS (days)	8.7±5.9	8.3±6.4	0.009	0.726*	11.5±12.9	11.6±9.1	0.188	0.291*	12.5±5.5	15.5±12.1	0.078	0.629*
Transfer to ICU =Yes	3 (10.7%)	5 (15.2%)	0.066	0.715**	2 (5.4%)	11 (11.8%)	0.097	0.347**	4 (17.4%)	34 (26.0%)	0.071	0.380
Mortal result =Yes	0 (0.0%)	0 (0.0%)	N/A	N/A	0 (0.0%)	2 (2.2%)	0.079	1.000**	2 (8.7%)	19 (14.5%)	0.060	0.742**

HNS: Hamilton-Norwood scale of androgenetic alopecia -HNS≥ 3 means Gabrin sign (+); CT: Computed tomography; SpO_2: Oxygen saturation by pulse oximeter; CURB-65: "confusion, urea, respiratory rate, blood pressure, age" at admission; LOS: Length of stay in hospital; ICU: Intensive care unit; N/A: Not applicable

† Patients without thoracic tomography were excluded from the analysis. ‡ Analyzed only among cases with pneumonia.

The Mann–Whitney U test* and Pearson's chi-square or Fisher's exact tests** were used. The effect sizes are Cramer's V (φc) for categorical variables and Cohen's d for scale variables. Results were presented as the mean±standard deviation or number of patients (column percentage). Significant values were shown in bold.

Table 3. Relationship of BPH in different age groups with hospitalization, CT results, and various prognostic indicators in COVID-19

Parameters	Group 2 (age of 50-64 years)				Group 3 (age of 65-75 years)			
	BPH		Effect size	p value	BPH		Effect size	p value
	No	Yes			No	Yes		
CT severity in confirmed all cases†			0.108	0.250			0.132	0.247
No pneumonia	32 (17.5%)	9 (16.4%)			8 (10.3%)	4 (4.9%)		
Mild-moderate pneumonia	111 (60.7%)	28 (50.9%)			42 (53.8%)	40 (48.8%)		
Severe pneumonia	40 (21.9%)	18 (32.7%)			28 (35.9%)	38 (46.3%)		
Prognostic indicators in confirmed all cases								
Asymptomatic=Yes	10 (4.9%)	2 (3.5%)	0.027	1.000**	6 (7.4%)	2 (2.4%)	0.136	0.099**
SpO_2 (%)	92.5±4.0	91.7±5.4	0.061	0.622*	89.6±7.1	88.5±6.0	0.301	0.056*
$SpO_2 \leq 93\%$	104 (51.0%)	31 (54.4%)	0.028	0.649	55 (67.1%)	65 (79.3%)	0.138	0.078
$SpO_2 < 90\%$	29 (14.2%)	9 (15.8%)	0.018	0.766	26 (31.7%)	41 (50.0%)	0.186	0.017
Pneumonia=Yes	152 (74.5%)	46 (80.7%)	0.060	0.475	71 (86.6%)	78 (95.1%)	0.148	0.058
CT = Severe pneumonia ‡	40 (26.5%)	18 (39.1%)	0.117	0.098	28 (40.0%)	38 (48.7%)	0.088	0.287
C-reactive protein (mg/dl)	48.9±59.0	74.8±95.5	0.266	0.033*	71.8±84.2	104.1±92.2	0.423	0.008*
C-reactive protein>40 mg/dl	73 (35.8%)	26 (45.6%)	0.084	0.176	38 (46.3%)	51 (62.2%)	0.159	0.042
Lymphocyte count<800/µl	50 (24.5%)	17 (29.8%)	0.050	0.417	41 (50.0%)	50 (61.0%)	0.157	0.157
Ferritin>500 ng/ml	66 (32.5%)	19 (33.3%)	0.007	0.907	38 (46.3%)	40 (49.4%)	0.030	0.698
d-dimer>1000 ng/ml	45 (22.2%)	15 (26.3%)	0.041	0.511	42 (51.2%)	50 (61.0%)	0.098	0.208
Hospitalization=Yes	94 (46.1%)	35 (61.4%)	0.127	0.041	57 (69.5%)	69 (84.1%)	0.173	0.026
Prognostic indicators in only confirmed inpatients								
CURB-65 score at admission	0.7±0.6	0.8±0.8	0.138	0.382	2.0±0.7	2.2±0.8	0.212	0.176
SpO_2 (%)	90.3±4.7	90.1±6.3	0.157	0.371*	87.8±7.8	87.3±5.7	0.237	0.185*
$SpO_2 \leq 93\%$	73 (77.7%)	23 (65.7%)	0.122	0.167	46 (80.7%)	61 (88.4%)	0.107	0.229
$SpO_2 < 90\%$	28 (29.8%)	8 (22.9%)	0.069	0.435	25 (43.9%)	41 (59.4%)	0.155	0.082
CT = Severe pneumonia ‡	33 (37.5%)	15 (48.4%)	0.097	0.288	27 (50.0%)	37 (56.9%)	0.069	0.451
C-reactive protein (mg/dl)	85.8 ±62.9	109.4±106.6	0.134	0.447	97.9±88.6	115.0 ±90.2	0.200	0.265
C-reactive protein>40 mg/dl	61 (64.9%)	23 (65.7%)	0.008	0.931*	36 (63.2%)	48 (69.6%)	0.068	0.448*
Lymphocyte count<800/µl	44 (46.8%)	16 (45.7%)	0.010	0.912	38 (66.7%)	47 (68.1%)	0.015	0.863
Ferritin>500 ng/ml	54 (58.1%)	18 (51.4%)	0.060	0.500	35 (61.4%)	39 (56.5%)	0.049	0.580
d-dimer>1000 ng/ml	37 (39.4%)	12 (34.3%)	0.047	0.597	41 (71.9%)	45 (65.2%)	0.072	0.420
LOS (days)	11.3±9.0	12.4±13.4	0.099	0.888*	13.6±11.2	14.2±10.1	0.079	0.658*
Transfer to ICU=Yes	8 (8.5%)	5 (14.3%)	0.085	0.338**	13 (22.8%)	15 (21.7%)	0.013	0.886
Mortal result=Yes	1 (1.1%)	1 (2.9%)	0.065	0.471**	10 (17.5%)	8 (11.6%)	0.085	0.342

BPH: Benign prostatic hyperplasia; CT: Computed tomography; SpO_2: Oxygen saturation by pulse oximeter; CURB-65: "confusion, urea, respiratory rate, blood pressure, age" at admission; LOS: Length of stay in hospital; ICU: Intensive care unit
† Patients without thoracic tomography were excluded from the analysis. ‡ Analyzed only among cases with pneumonia.
The Mann–Whitney U test* and Pearson's chi-square or Fisher's exact tests** were used. The effect sizes are Cramer's V (φc) for categorical variables and Cohen's d for scale variables. Results were presented as the mean±standard deviation or number of patients (column percentage). Significant values were shown in bold.

The prognostic value of BPH was shown in **Table 3**. When it was examined from a broad perspective, it was noticed that generally much smaller effect sizes were achieved in the middle-aged group compared to elderly patients. However, similar statistical significances were recorded in both groups. Hospitalization frequencies were significantly higher in patients with BPH in both groups, with small-medium effect sizes (φc=0.127, p=0.041; φc=0.173, p=0.026; respectively).In both groups, CRP values were significantly higher in patients with BPH (p=0.033, p=0.008; respectively). However, CRP significantly exceeded the cut-off value of 40 mg/dl only in elderly patients with BPH (p=0.042). Moreover, in elderly patients, SpO_2 was found significantly more frequently to be lower than 90% in those with BPH (p=0.017). No relationship was found between any prognostic parameter and BPH in any group consisting of inpatients. Indeed, it was remarkable that BPH had no relationship with transfer to ICU and mortality.

Results of prior and post-hoc power analysis in the research on the prognostic value of AGA severity and BPH in patients with COVID-19 were presented in **Table S1** and **Table S2**. Unfortunately, the number of patients required for sufficient power in many parameters could not be reached due to the very small effect sizes. In the analysis investigating the prognostic value of AGA severity, the achieved power was between 59-99% in the parameters with significant results, but the achieved power in hospitalization frequency, which is the primary endpoint, was only 31.9%. In the analysis investigating the prognostic value of BPH, the achieved power in hospitalization frequency with significant results remained at 54-60%.

Table S1. Results of priori and post-hoc power analysis in research on the prognostic value of AGA severity in patients with COVID-19

Parameters	df	Group 1 (AGA in age of 30-49 years)				Group 2 (AGA in age of 50-64 years)				Group 3 (AGA age of 65-75 years)			
		Effect size	Total sample size		Achieved power	Effect size	Total sample size		Achieved power	Effect size	Total sample size		Achieved power
			Available	Required†			Available	Required†			Available	Required†	
CT severity in confirmed all cases ‡	2	0.078	252	1584	18.2%	0.103	239	909	27.7%	0.040	191	6022	7.4
Various prognostic indicators in confirmed all cases													
Asymptomatic =Yes	1	0.025	306	12559	7.2%	0.002	262	>1.9 million	5.0%	0.017	194	27159	15.4
SpO_2 (%)	-	0.053	309	11718	7.4%	0.250	262	598	45.6%	0.067	195	14068	6.3%
SpO_2≤93%	1	0.072	309	1515	24.4%	0.141	262	395	62.6%	0.041	195	4670	8.8%
SpO_2<90%	1	0.039	309	5161	10.5%	0.087	262	1037	29.1%	0.009	195	96900	5.2%
Pneumonia =Yes	1	0.084	309	1113	31.5%	0.044	262	4055	11.0%	0.011	195	64867	5.3%
CT = Severe pneumonia §	1	0.038	174	5436	7.9%	0.106	198	699	32.0%	0.021	176	17798	5.9%
C-reactive protein (mg/dl)	-	0.045	309	16252	6.7%	0.198	262	952	31.1%	0.201	195	1566	16.6%
C-reactive protein>40 mg/dl	1	0.035	309	6408	9.4%	0.081	262	1197	25.9%	0.156	195	323	58.7%
Lymphocyte count<800/µl	1	0.013	309	46443	5.6%	0.154	262	331	70.3%	0.031	195	8168	7.2%
Ferritin>500 ng/ml	1	0.022	309	16217	6.7%	0.104	261	726	39.0%	0.009	194	96900	3.8%
d-dimer>1000 ng/ml	1	0.051	308	3018	14.6%	0.010	261	78489	5.3%	0.049	195	3269	10.5%
Hospitalization =Yes	1	0.026	309	11611	7.4%	0.092	262	928	31.9%	0.024	195	13627	6.3%
Various prognostic indicators in only confirmed inpatients													
CURB-65 score at admission	-	0.035	61	27008	5.2%	0.143	130	1409	11.0%	0.039	154	42560	5.3%
SpO_2 (%)	-	0.393	61	218	31.2%	0.262	130	590	25.8%	0.143	154	3166	9.5%
SpO_2≤93%	1	0.136	61	425	31.2%	0.220	130	163	77.9%	0.001	154	>7 million	5.0%
SpO_2<90%	1	0.123	61	519	28.9%	0.058	130	2334	10.2%	<0.001	154	>8 million	5.0%
CT = Severe pneumonia §	1	0.002	58	>1.9 million	5.0%	0.075	120	1396	13.0%	0.001	147	>7 million	5.0%
C-reactive protein (mg/dl)	-	0.115	61	2504	7.2%	0.382	130	128	99.7%	0.405	154	43	99.8%
C-reactive protein>40 mg/dl	1	0.004	61	490554	5.0%	0.043	130	4245	7.8%	0.252	154	124	87.9%
Lymphocyte count<800/µl	1	0.035	61	6408	5.9%	0.115	130	594	25.8%	0.027	154	10767	6.3%
Ferritin>500 ng/ml	1	0.163	61	296	24.7%	0.083	129	1140	15.7%	0.082	154	1168	17.4%
d-dimer>1000 ng/ml	1	0.099	61	801	12.1%	0.002	130	>1.9 million	5.0%	0.011	154	64867	5.2%
LOS (days)	-	0.009	60	407880	5.0%	0.188	127	1142	15.3%	0.078	153	10642	6.3%
Transfer to ICU =Yes	1	0.032	61	7665	8.1%	0.097	130	835	19.8%	0.071	154	1558	14.3%
Mortal result =Yes	1	-	61	-	N/A	0.079	130	1258	14.7%	0.060	154	2181	11.6%

The column variables are dichotomous with HNS ≤2 and HNS≥3 (Gabrin sign)
AGA: Androgenic alopecia; HNS: Hamilton-Norwood scale of androgenetic alopecia; CT: Computed tomography; SpO_2: Oxygen saturation by pulse oximeter; CURB-65: "confusion, urea, respiratory rate, blood pressure, age" at admission; LOS: Length of stay in hospital; ICU: Intensive care unit; N/A: Not applicable
† It is the number of patients required for α=0.05, power (1- β) = 0.80 at a confidence level of 95%. ‡ Patients without thoracic tomography were excluded from the analysis. § Analyzed only among cases with pneumonia.
The effect sizes are Cramer's V (φc) for categorical variables and Cohen's d for scale variables. The variables with statistical significance shown in Table 2 were written in bold.

Table S2. Results of priori and post-hoc power analysis in research on the prognostic value of BPH in patients with COVID-19

Parameters	df	Group 2 (BPH in age of 50-64 years)				Group 3 (BPH in age of 65-75 years)			
		Effect size	Total sample size		Achieved power	Effect size	Total sample size		Achieved power
			Available	Required†			Available	Required†	
CT severity in all confirmed cases ‡	2	0.108	238	827	30.0%	0.132	160	553	30.1%
Various prognostic indicators in all confirmed cases									
Asymptomatic=Yes	1	0.027	261	10767	7.2%	0.136	163	425	55.5%
SpO_2 (%)	-	0.061	261	12942	6.8%	0.301	164	366	49.8%
SpO_2≤93%	1	0.028	261	10012	7.4%	0.138	164	413	42.4%
SpO_2<90%	1	0.018	261	24225	6.0%	0.186	164	227	66.4%
Pneumonia=Yes	1	0.060	261	2181	16.3%	0.148	164	359	47.4%
CT = Severe pneumonia §	1	0.117	197	574	37.6%	0.088	148	1014	18.8%
C-reactive protein (mg/dl)	-	0.266	261	684	40.9%	0.423	164	186	74.9%
C-reactive protein>40 mg/dl	1	0.084	261	1113	27.4%	0.159	164	311	53.0%
Lymphocyte count<800/µl	1	0.050	261	3140	12.7%	0.157	164	319	52.0%
Ferritin>500 ng/ml	1	0.007	260	160181	5.2%	0.030	163	8721	6.7%
d-dimer>1000 ng/ml	1	0.041	260	4670	10.2%	0.098	164	818	24.1%
Hospitalization=Yes	1	0.127	261	487	53.7%	0.173	164	263	60.0%
Various prognostic indicators in only confirmed inpatients									
CURB-65 score at admission	-	0.138	129	2186	10.4%	0.212	126	742	20.9%
SpO_2 (%)	-	0.157	129	1690	12.0%	0.237	126	594	25.0%
SpO_2≤93%	1	0.122	129	528	28.3%	0.107	126	686	22.5%
SpO_2<90%	1	0.069	129	1649	12.3%	0.155	126	327	41.3%
CT = Severe pneumonia §	1	0.097	119	835	18.5%	0.069	119	1649	11.7%
C-reactive protein (mg/dl)	-	0.134	129	2318	5.0%	0.200	126	832	19.2%
C-reactive protein>40 mg/dl	1	0.008	129	122639	5.1%	0.068	126	1698	11.9%
Lymphocyte count<800/µl	1	0.010	129	78489	5.2%	0.015	126	34884	5.3%
Ferritin>500 ng/ml	1	0.060	128	2181	10.4%	0.049	126	3264	8.5%
d-dimer>1000 ng/ml	1	0.047	129	3554	8.3%	0.072	126	1515	12.8%
LOS (days)	-	0.099	129	4244	7.7%	0.079	125	5320	7.1%
Transfer to ICU=Yes	1	0.085	129	1087	16.2%	0.013	126	46443	5.2%
Mortal result=Yes	1	0.065	129	1858	11.4%	0.085	126	1087	15.9%

The column variables are dichotomous with BPH (-) and BPH (+).
BPH: Benign prostatic hyperplasia; CT: Computed tomography; SpO_2: Oxygen saturation by pulse oximeter; CURB-65: "confusion, urea, respiratory rate, blood pressure, age" at admission; LOS: Length of stay in hospital; ICU: Intensive care unit
† It is the number of patients required for α=0.05, power (1- β) = 0.80 at a confidence level of 95%. ‡ Patients without thoracic tomography were excluded from the analysis. § Analyzed only among cases with pneumonia.
The effect sizes are Cramer's V (φc) for categorical variables and Cohen's d for scale variables. The variables with statistical significance shown in Table 3 were written in bold.

DISCUSSION

The increase in androgen-induced TMPRSS2 expression in the lung is considered a critical place in prognosis (9,16). A clinical relationship between AGA and BPH has been reported (23). Therefore, it is reasonable that both diseases may indicate the level of androgen receptor signaling in the lung. The biomarkers that have been reported to be useful in predicting COVID-19 prognosis in various meta-analyzes are as follows: CRP, d-dimer, ferritin, lymphocyte count, lymphocyte subsets, white blood cell count, neutrophil count, platelet count, prothrombin time, fibrinogen, lactate dehydrogenase, procalcitonin, erythrocyte sedimentation rate (24,25). The cut-off values of these poor prognostic measures are affected by ethnic differences, and there is no consensus on the cut-off values of most of them (26,27). In our study, many clinical and laboratory criteria, primarily hospitalization, were used to test the hypothesis. Although the prognosis of COVID-19 is closely related to many confounders such as age, comorbidities, drugs, smoking, and BMI, it is seen in **Table 1** that the sterility targeted in the study protocol was reached at a reasonable level. Wambier et al. (28) pointed out that 67% of 122 men with COVID-19, most of whom were hospitalized for low saturation, had clinically relevant AGA. They proposed the androgen-mediated COVID-19 severity hypothesis based on a report in the literature that the prevalence of severe AGA in age-matched men was 31% to 53% in a similar white population (29,30). In memory of Dr. Gabrin (31), who was the first doctor in the United States to die of COVID-19, they proposed using the "Gabrin sign" to visually identify patients at higher risk for severe symptoms after COVID-19 infection. The preliminary observational findings from the violin plot suggested that the Gabrin effect might be valid (**Figure 2**). Although the Gabrin sign was found to be unrelated to the frequency of hospitalization, it prevented us from refusing the prognostic significance of the severe AGA phenotype due to our following findings: distribution pattern of severe AGA frequency by age in followed-up patients observed in the violin plot, inadequate achieved power for many parameters, significant relationship with few prognostic markers such as SpO_2, CRP, and lymphocyte count in both all patients and inpatients in groups other than in young patients, and consistently higher frequencies of poor prognostic markers in patients with severe AGA. The weakness of power analysis is that the effect sizes are usually very small. This strengthens the opinion that the Gabrin sign will make little, even if significant, or no contribution to predicting clinical outcomes (hospitalization, transfer to ICU, LOS, mortality).

It was found that there was a significant increase in the frequency of hospitalization in patients with BPH. However, this difference was not significant in hospitalized patients. Like AGA, sufficient power was not reached, and no relationship was found between clinical outcomes and BPH. However, recording small-medium effect sizes in many parameters unlike AGA, which is more evident in elderly patients, strengthens the possibility that the prognostic significance of BPH is more pronounced than AGA. In a study conducted on male inpatients with COVID-19 pneumonia, Karabulut et al. (31) reported that those with BPH had significantly higher ICU needs and mortality rates than those without it. On the contrary, Topaktaş et al. (32) reported lower mortality in patients with BPH. Although our study was conducted with a larger sample size; our findings were incompatible with the former study. We think that the contradictory aspects of our study arise from the design of previous studies. Because although age was adjusted in studies, not categorizing age causes Simson's paradox. Besides, comorbidities and current medications were not taken into consideration in patient selection.

The study has some advantages and limitations. To the best of our knowledge, this is the largest prospective study to investigate the prognostic significance of AGA and BPH in COVID-19. Prospective follow-up of not only inpatients but also outpatients according to the study protocol, adjusting the confounders, post-hoc power analysis of the results, and investigation of the prognostic value of both AGA and BPH make this study unique and comprehensive. Although we have reached sufficient power only in BPH to evaluate the frequency of hospitalization, which is our primary endpoint, it was noted that excessive numbers of patients were required for the accurate interpretation of many parameters. Therefore, the most important limitation of the study is the high rate of type 2 error (β). The lack of a comprehensive publication from our country on the validity of the cut-off values we prefer for prognostic biomarkers damages the reliability of our results. Our results are still noteworthy as the effect size, which is independent of sample size provided that there is a similar distribution, allows us to evaluate the clinical significance of the relevant parameter.

CONCLUSION

Since sufficient power was not achieved in interpreting the clinical outcomes except hospitalization, we could not provide a definite opinion on these issues for both AGA and BPH. When our results were evaluated together with effect sizes, we found some evidence that both AGA and BPH are of prognostic significance, particularly in patients over 50 years old. BPH may indicate the need

for hospitalization. On the other hand, we concluded that the Gabrin sign would not be useful in practice due to very small effect sizes. The absence of any relationship with the most important prognostic indicators such as transfer to ICU and mortality in both AGA and BPH suggests that they will not be useful prognostic criteria in hospitalized patients. Nevertheless, we believe that investigating the epigenetic and hormonal differences by sex in the pathogenesis of COVID-19 can lead to inspiring results in the search for treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the local ethics committee (Date: 19.10.2020, Decision No: 2020/19-185) and the Scientific Research Platform of the Ministry of Health (2020-09-18T11_21_01).

Informed Consent: Informed consent forms were obtained from all 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.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, et al. China Medical Treatment Expert Group for COVID-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-20.
2. Jin JM, Bai P, He W, et al. Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health 2020; 8: 152.
3. vom Steeg LG, Klein SL. SeXX Matters in Infectious Disease Pathogenesis. PLoS Pathog 2016; 12: e1005374.
4. Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. J Am Acad Dermatol 2020; 83: 308-9.
5. Wambier CG, Vaño-Galván S, McCoy J, Pai S, Dhurat R, Goren A. Androgenetic alopecia in COVID-19: compared to age-matched epidemiologic studies and hospital outcomes with or without the Gabrin sign. J Am Acad Dermatol 2020; 83: e453-4.
6. Nielsen HC, Zinman HM, Torday JS. Dihydrotestosterone inhibits fetal rabbit pulmonary surfactant production. J Clin Invest 1982; 69: 611-16.
7. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271-80
8. Lucas JM, Heinlein C, Kim T, et al. The androgen-regulated protease TMPRSS2 activates a proteolytic cascade involving components of the tumor microenvironment and promotes prostate cancer metastasis. Cancer Discov 2014; 4: 1310-25.
9. Asselta R, Paraboschi E, Mantovani A, Duga S. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY) 2020; 12: 10087-98.
10. Wambier CG, Goren A, Vaño-Galván S, et al. Androgen sensitivity gateway to COVID-19 disease severity. Drug Dev Res 2020; 81: 771-76.
11. Bennett CL, Price DK, Kim S, et al. Racial variation in CAG repeat lengths within the androgen receptor gene among prostate cancer patients of lower socioeconomic status. J Clin Oncol 2002; 20: 3599-604.
12. McCoy J, Wambier CG, Vano-Galvan S, et al. Racial variations in COVID-19 deaths may be due to androgen receptor genetic variants associated with prostate cancer and androgenetic alopecia. Are anti-androgens a potential treatment for COVID-19? J Cosmet Dermatol 2020; 19: 1542-43.
13. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). Ann Oncol 2020; 31: 1040-45.
14. Severe COVID-19 GWAS Group, Ellinghaus D, Degenhardt F, et al. Genomewide association study of severe COVID-19 with respiratory failure. N Engl J Med 2020; 383: 1522-34.
15. Lai J-J, Chang P, Lai K-P, Chen L, Chang C. The role of androgen and androgen receptor in skin-related disorders. Arch Dermatologic Res 2012; 304: 499-510.
16. Bhowmick NA, Oft J, Dorff T, et al. COVID-19 and androgen-targeted therapy for prostate cancer patients. Endocr Relat Cancer 2020; 27: R281-R92.
17. Republic of Turkey Ministry of Health, General Directorate of PublicHealth. COVID-19 (SARS-CoV2 Infection) Guide (Coronavirus Science Board Study): 2020. Available at: https://covid19.saglik.gov.tr/Eklenti/39061/0/covid-19rehberieriskinhastatedavisipdf.pdf. Published (June 4, 2020). Updated (September 17, 2020). Accessed (February 28, 2021).
18. Sarıkaya K, Senocak C, Sadioglu FE, Bozkurt ÖF. Is combined topical-local anesthesia technique adequate for visual internal urethrotomy in the treatment of traumatic posterior urethral strictures and prostatic urethral stenoses? Ulus J Trauma Emerg Surg 2021; 27: 139-45.
19. Wang B, Wu P, Kwan B, Tu XM, Feng C. Simpson's Paradox: Examples. Shanghai Arch Psychiatry 2018; 30: 139-43.
20. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G* Power 3.1: Tests for correlation and regression analyses. Behav Res Methods 2009; 41: 1149-60.
21. Lenhard W, Lenhard A. Calculation of Effect Sizes. 2016 Available at: https://www.psychometrica.de/effect_size.html. Dettelbach (Germany): Psychometrica.Accessed (28 February 2021).
22. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. J Exp Psychol Gen 2012; 141: 2-18.
23. Monib KME, Hussein MS, Kandeel WS. The relation between androgenetic thin hair diagnosed by trichoscope and benign prostatic hyperplasia. J Cosmet Dermatol 2019; 18: 1502-6.
24. 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.
25. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020; 58: 1021-28.

26. Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis 2020; 96: 467-74.
27. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-62. *Erratum in: Lancet 2020; 395: 1038.*
28. Wambier CG, Vaño-Galván S, McCoy J, et al. Androgenetic alopecia present in the majority of patients hospitalized with COVID-19: The "Gabrin sign". J Am Acad Dermatol 2020; 83: 680-2.
29. Severi G, Sinclair R, Hopper JL, et al. Androgenetic alopecia in men aged 40-69 years: prevalence and risk factors. Br J Dermatol 2003; 149: 1207-13.
30. Goren A, Vaño-Galván S, Wambier CG, et al. A preliminary observation: Male pattern hair loss among hospitalized COVID-19 patients in Spain - A potential clue to the role of androgens in COVID-19 severity. J Cosmet Dermatol 2020; 19: 1545-47.
31. Karabulut I, Cinislioglu AE, Cinislioglu N, et al. The effect of the presence of lower urinary system symptoms on the prognosis of COVID-19: preliminary results of a prospective study. Urol Int 2020; 104: 853-58.
32. Topaktaş R, Tokuç E, Ali Kutluhan M, Akyüz M, Karabay E, Çalışkan S. Clinical features and outcomes of COVID-19 patients with benign prostatic hyperplasia in ageing male: A retrospective study of 18 cases. Int J Clin Pract 2020; 74: e13574.

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Evaluation of occupational exposure reasons and experiences of nursing students

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ABSTRACT

Aim: The aim of this study was to describe the occupational exposure reasons and experiences of nursing students.

Material and Method: The qualitative research design was used. The participants were selected using the purposive sampling method. The 20 nursing students included in this study. The data was collected at face-to-face interviews conducted during September 2019 and February 2020.

Results: The mean age of nursing students was 21.65±0.91. The majority (85%) of nursing students were women, and 15% were men (n=3). From the interviews, six key themes were identified regarding the nursing students' experiences of occupational exposure in the last six months: lack of knowledge, inadequate experience, theoretical and practical training loads, inadequate resources, lack of warning and information, and carelessness.

Conclusion: The one of the most important reasons for exposure to occupational hazards is lack of knowledge. Nursing Schools should ensure that nursing students are adequately trained in occupational hazards before their clinical placements.

Keywords: Occupational hazards, nursing students, qualitative research

INTRODUCTION

The nursing profession is an applied discipline, and one of the most important parts of nursing education is clinical training (1,2). It is essential for both the personal development and the practice skills development of nursing students (1,2). Nursing students participate in all patient care activities and are exposed to the same occupational risks as nurses, since practical training is carried out in real clinical environments with patients (2). Previous studies showed that nursing students faced all occupational hazards, including biological, chemical, ergonomic, physical, and psychological, during their practical training (3-7).

Unlike nurses, nursing students are only in clinical environments during their practical training. Even if they are less experienced, they still perform all interventional practices like nurses and work with many sharp devices (needle, lancet, etc.) (8). Previous studies found that the group most exposed to needle-stick injuries was nursing students among healthcare workers (9,10). The study conducted among nursing students by Çakar et al. (11) showed needle-stick injury rate was 27.8%. Doğru et al. (12) found that nursing students' needle-stick injury rate was 31%.

Another occupational exposure experienced by nursing students is musculoskeletal disorders. Literature showed that 66.23% of nursing students felt pain, discomfort and numbness in their neck (13). Abledu et al. (14) reported that 70.1% of nursing students experienced musculoskeletal disorders in the last 12 months, and 56.1% experienced a loss of function (14).

Nursing students face many types of violence, such as physical and verbal abuse, in their clinical environments (15). Almost half of nursing students are exposed to work-related violence (16). Magnavita et al. (17) reported that 43% of nurses and 34% of nursing students were exposed to physical or verbal violence. Amare et al. (18) showed that 66.2% of nursing students were exposed to biological hazards, 66.2% to physical, 84.8% to mechanical and 92.7% to psychological hazards. Many studies show the occupational exposures experienced by nursing students. To prevent this exposure and correctly structure occupational health and safety education programs, the causes of these exposures should be defined. Therefore, the aim of this study was to describe the reasons for occupational exposure and experiences of nursing students.

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MATERIAL AND METHOD

In order to carry out the study, approval was obtained from the Ege University Scientific Research and Publication Ethics Committee (Date: 29.08.2019, Decision No: 09/04-341) and the institution where the study was conducted. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was taken from the nursing students fulfilling inclusion criteria and accepting to participate in the study.

Study Design and Sampling

This study used a qualitative research design to describe the reasons for occupational exposure and experiences of nursing students. The participants were selected using the purposive sampling method. The 20 nursing students who experienced at least one of biological, physical, musculoskeletal, chemical and psychosocial occupational hazards in last six months and agreed to participate in the study were included in the study.

Data Collection

The data was collected at face-to-face interviews conducted during September 2019 and February 2020, and each lasted between 30 and 60 minutes. In-depth face-to-face interviews were audio recorded. Data collection continued until the same concepts started to appear. To ensure privacy, the interviews were conducted in a quiet, secluded place at the nursing school. Interviews were conducted by a researcher. During the interviews, participants were given the opportunity to talk openly about their experiences. Before the interviews started, the nursing students were informed about the aim of the study and their consent was obtained. The interviewers used a semi-structured framework that was developed based on a literature review.

Semi-structured interview framework

1. What occupational exposure(s) have you experienced during practical trainings in the last six months?
2. What do you think are the reasons for the occupational exposure(s) you experience?
3. What can be done to prevent or reduce occupational exposures?

Place/Time of Study

Study was conducted between September 2019 and February 2020 with nursing students enrolled XXX University, Faculty of Nursing.

Data Analyses

Recorded data was documented through verbatim transcription. A categorization matrix was created based on the data, and all data was examined and coded according to the categories. All steps of the study were explained in detail; data was described in detail, emerging themes were exemplified by direct quotes, and what the participants said was exactly described.

RESULTS

The mean age of nursing students was 21.65±0.91. The majority (85%) of nursing students were women, and 15% were men (n=3). Of these students, eight (40%) were in the second year, six (30%) were in the third year, and six (30%) were in the fourth year (**Table 1**). From the interviews, six key themes were identified regarding the nursing students' experiences of occupational exposure in the last six months: lack of knowledge, inadequate experience, theoretical and practical training loads, inadequate resources, lack of warning and information, and carelessness.

Table 1. Nursing students characteristics

Characteristics (N=20)	n	%
Age (Mean±SS)	21.65±0.91	
Gender		
Women	17	85
Men	3	15
Year of Study		
Second year	8	40
Third year	6	30
Fourth year	6	30

Lack of Knowledge

Nursing students stated that they did not have enough information about occupational hazards, use of personal protective equipment, and occupational accident notifications. Some students reported that they were not aware of the occupational exposures they experienced because they did not have enough information about occupational hazards.

"*While I was in the oncology clinic, some of the drug was spilled during drug administration. Since I did not know how to clean an antineoplastic drug, I cleaned it with gauze. I would never have done this if I had known it was harmful to my health.*" (Nursing student, 2)

Some students reported that they did not know they should not recap the needles after using them.

"*After applying the patient's treatment, I experienced a needle-stick injury while recapping the needle. Actually, I didn't need to recap the needle while I put it in the sharp box, but I didn't know that. I learned after the accident*" (Nursing student, 9)

Some students stated that they did not have enough information about the process of reporting occupational exposures.

"*I should have notified the Occupational Health and Safety Unit within three working days of the accident date. But I didn't know this. I have learned after the work accident.*" (Nursing student, 3)

Inadequate Experience

Some students stated that their occupational exposures were due to their insufficient professional experience. Students stated that they tried to act quickly in order to be able to act together with the team and not miss the parenteral administrations; however, because they did not have enough experience, this situation caused them to be exposed to physical hazards such as falling, tripping, and especially sharps-related injuries. Some students stated that the needle-stick injury they experienced during their first interventional practice was due to their lack of experience.

"*We had been applying treatments to the patients along with nurses. The nurses left the room, and I did not want to be left behind. I stuck a needle in my hand while trying to act fast.*" (Nursing student, 5)

"*I was going to do an intramuscular injection for the first time, but I think I got excited. After I injected the drug into the patient, I stuck the needle in my hand.*" (Nursing student, 1)

Students stated that they experienced musculoskeletal disorders due to lack of experience in situations where appropriate body mechanics such as carrying, lifting and positioning patients should be used.

"*While I was lifting the patient from his bed, I felt all the weight of the patient on my body. Then, I suddenly felt a pain in my back. I suffered back pain for two days.*" (Nursing student, 10)

Theoretical and Practical Training Loads

Students stated that the intensity of the theoretical and practical training caused them to experience occupational exposure. In particular, intern nursing students reported that in addition to working as a clinical nurse four days a week, the final exams and homework loads related to their internship caused them to experience occupational exposure.

"*Being an intern nursing student is truly hard. You are like a nurse working in a clinic, but on the other hand, you have lessons to pass. The final exam weeks are especially hard; I stuck a needle in my hand while I was taking blood from the patient.*" (Nursing student, 20)

"*On the one hand, I was trying to do patient's treatment; on the other hand, I was trying to catch up during the nurses' shift change. Normally, when the three-way stopcock is clogged, I do not force the medicine. However, I was so busy that I could not think at that moment. It splashed in my eyes due to the pressure.*" (Nursing student, 17)

Inadequate Resources

Students stated that they experienced occupational exposures due to the lack of adequate and appropriate personal protective equipment in the clinical settings.

"*I know I have to wear gloves when drawing blood, but I cannot use them because the gloves are too big. While I was taking blood, the patient's blood got on my hand. There was an open wound on my hand.*" (Nursing student, 11)

"*I was just watching the surgical procedure. Suddenly, blood from the child splashed in my eyes. If I had worn glasses, I would not have experienced this. However, there were no goggles in the clinic. Unfortunately, we are having difficulties in obtaining some personal protective equipment.*" (Nursing student, 8)

"*There was a patient in contact isolation. We went to the patient's room with the nurse for treatment. As the available personal protective equipment was insufficient, only the nurse wore personal protective equipment. She said to me, 'You do not touch anything. I will do it; you will only help me.' However, this was not possible. I touched everything just like her.*" (Nursing student, 14)

Lack of Warning and Information

Students stated that they were not adequately informed about occupational hazards in the clinic by nurses during clinical placements

"*....., There was the patient who had a diagnosis of scabies in the clinic. Nobody informed us and we took care of the patient all day.*" (Nursing student, 6)

"*I entered the room of the patient diagnosed with tuberculosis without a mask to take his blood pressure. Nurses could have informed me that the patient was with tuberculosis.*" (Nursing student, 13)

Nursing students stated that when they experienced any work accidents in clinical settings, other members of the health care team did not act sensitively in dealing with them.

"*I had a work accident in the clinic and immediately told the nurse. But the nurse didn't care. I was very nervous and stressed because I had had a work accident. The nurse could have directed me to the occupational health and safety unit, but she didn't it.*" (Nursing student, 4)

Carelessness

Students stated that they were exposed to occupational hazards because they or their friends did not act carefully in clinical settings.

"*We were preparing treatment in the treatment room. Someone put the needle there after using it. I didn't even understand how it was. The needle stuck in my hand. I don't know whether it was the needle contaminated. Maybe it only was used for preparing the treatment.*" (Nursing student, 15)

"*I was in public health placement. Two patients came. I administrated the intravenous drug to one and dressed the other one. I put the injector there after intravenous medication administration. Unfortunately, When I was collecting the dressing materials that needle stuck in my hand. It was all because of my carelessness. I should have put the needle in the sharp box after using it.*" (Nursing student, 7)

DISCUSSION

In this study, nursing students reported a lack of knowledge as the reason for exposure to occupational hazards, such as needle-stick injuries, ergonomic hazards, etc. Amare et al. (18) found that most of the nursing students had insufficient knowledge about occupational hazards during clinical practice and experienced needle-stick injuries due to insufficient adherence to standard precautions. Attia et al. (19) found that one of the reasons for occupational hazard exposure is the lack of occupational health and safety education. One of the most common hazards encountered by nursing students is needle-stick injuries, frequently caused by the recapping of needles after use (20,21). Suliman et al. (22) stated that 46.2% of nursing students do not know that they should not recap the needle after use. In this study, nursing students stated that they experienced a needle-stick injury while recapping the needles after use and they experienced exposure to occupational hazards without realizing it because they did not know enough about the risks involved in certain situations. Nursing students are informed about occupational health and safety before clinical placement by their own educational institutions or practice institutions, but they do not have enough awareness about occupational hazards. For this reason, more training about occupational hazards and the use of personal protective equipment should take place in the occupational health and safety training given to nursing students.

Nursing students are vulnerable to occupational hazards due to insufficient manual skills and lack of clinical experiences (19,23). Previous studies showed that nursing students were exposed to needle-stick injuries during invasive procedures because they were stressed and inexperienced (19,24). In this study, nursing students stated that they were exposed to needle-stick injuries and physical and ergonomic hazards due to lack of experience. It is thought that this may be because nursing students do not have sufficient laboratory practice before their clinical placements. It is recommended that students' manual skills be developed with active learning methods, such as simulations, before clinical placement and that they be provided support by clinical instructors, especially in the first year of clinical placement.

In this study, nursing students stated that the intensity of theoretical and practical training caused them to be exposed to occupational hazards. Especially intern nursing students stated that they felt this intensity more. Eyi et al. (1) determined that workload is one of the most important causes of exposure to occupational hazards. Nursing education has a very intensive curriculum that combines theory and practice. In order to reduce exposure to occupational hazards, it is recommended that the intensity of theoretical and practical nursing training should be established in line with the Nursing Core Curriculum.

Personal protective equipment is one of the most important measures in preventing or reducing occupational exposures. Attia et al. (19) found that 57% of nursing students stated the lack of personal protective equipment as one of the risk factors for occupational exposure. Amare et al. (18) stated that 37.7% of nursing students experienced needle-stick injuries, and this may be due to the lack of personal protective equipment. Another reason for occupational exposure expressed by nursing students in this study is the inadequacy of personal protective equipment. It is thought that this situation may be due to the limitation of nursing practice areas and the increase in the number of students in the clinics.

Another reason for occupational exposure expressed by nursing students in this study is insufficient warnings and information. Nursing students who are trying to gain clinical practice skills and create their professional identities in a high-risk working environment are faced with many health hazards and need support. In order to prevent occupational exposures, nursing students, who are part of the healthcare team and participate in all practices in the clinics, should be properly informed about occupational hazards.

Another important point to prevent occupational hazards exposure is timely notification of work accidents. However, previous studies reported that notifications are either not made at all or not timely (22,25). In this study, nursing students stated that they were not properly guided by nurses after experiencing a work accident. It should be ensured that nurses and other members of the healthcare team accept nursing students as part of the healthcare team.

Previous studies showed that carelessness was one of the most important causes of exposure to occupational hazards (26,27). In the study conducted by Eyi et al. (1), carelessness also played a major role in occupational accidents. Al Qadire et al. (20) found that one of the major causes of needle-stick injuries was talking to others. Nursing students, in this study, stated that they experienced occupational hazard exposure due to the

carelessness of their friends or other healthcare team members. The reason for this may be that nursing students and health professionals did not comply with the standard precautions sufficiently.

CONCLUSION

In this study, the experiences of nursing students' occupational exposure were evaluated. The study provided information about the reasons for nursing students' occupational exposures. From the nursing students' points of view, lack of knowledge, inadequate experience, theoretical and practical training loads, lack of warning information, inadequate resources and carelessness were the primary causes of occupational exposure.

Nursing schools play a crucial role in preventing occupational exposure to nursing students. They should ensure that nursing students are adequately trained in occupational hazards before their clinical placements. Additionally, nursing schools should ensure this training is continued by clinical instructors during clinical placements.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ege University Scientific Research and Publication Ethics Committee (Date: 29.08.2019, Decision No: 09/04-341)

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

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Eyi S, Eyi İ. Nursing students' occupational health and safety problems in surgical clinical practice. SAGE Open 2020; 10: 1.
2. Moghaddam HR, Aghamohammadi V, Jafari M, Absalan M, Nasiri K. Challenges faced by nursing students to work with nursing personnel: A qualitative study. Adv Med Educ Prac 2020; 11: 313.
3. Huang H, Yi Q, Tang S, An R. Occupational exposure among Chinese nursing students: current status, risking factors and preventive interventions. Int J Clin Experiment Med 2016; 8: 16578-86.
4. Akan A, Toyran M, Erkoçoğlu M, Kaya A, Kocabaş C. The prevalence of allergic contact sensitization of practicing and student nurses. Int J Occup Environ Med 2012; 3: 1.
5. Boucaut R, Cusack L."Sometimes your safety goes a bit by the wayside": Exploring occupational health and safety with student nurses. Nurse Educ Pract 2016; 20: 93–8.
6. Tao X, Peng H, Qian L, et al. Occupational exposure to positive blood and body fluids among health care workers in a Chinese university hospital: a three years retrospective study. Glob J Health Sci 2017; 9: 157-62.
7. Visser MJ, Verberk, MM, van Dijk, FJ, Bakker JG, Bos JD, Kezic S. Wet work and hand eczema in apprentice nurses; part I of a prospective cohort study. Contact Dermatitis 2014; 70: 44-55.
8. Cheung K, Ching SSY, Chang KKP, Ho SC. Prevalence of and risk factors for needlestick and sharps injuries among nursing students in Hong Kong. Am J Infect Control 2012; 40: 997-1001.
9. Hada V, Saurabh K, Sharma A, Nag VL, Gadepalli RS, Maurya AK. Nursing students: a vulnerable health-care worker for needlesticks injuries in teaching hospitals. J Fam Med Prim Care 2018; 7: 717.
10. Trivedi A, Kasar PK, Tiwari R, Verma P, Sharma A. An educational interventional programme for prevention and management of needle stick injuries among nursing students at a tertiary care hospital, Jabalpur, Madhya Pradesh. Natl J Community Med 2013; 4: 132–6.
11. Çakar M, Şişman NY, Oruç D. Hemşirelik Öğrencilerinin klinik uygulamalarında karşılaştıkları sağlık riskleri. Dokuz Eylül Üniversitesi Hemşirelik Fakültesi Elektronik Derg 2019; 12: 2.
12. Doğru BV, Akyol, A. Hemşirelik öğrencilerinde kesici ve delici alet yaralanmalarının değerlendirilmesi. Acıbadem Üniversitesi Sağlık Bilimleri Derg 2018; 1: 59-66.
13. Firmino CF, Sousa LMM, Marques JM, et al. Prevalence of musculoskeletal symptoms in nursing students. BMC Health Services Res 2018; 18: 54.
14. Abledu JK, Offei EB. Musculoskeletal disorders among first-year Ghanaian students in a nursing college. African Health Sci 2015; 15: 444-9.
15. Seibel M. For us or against us? Perceptions of faculty bullying of students during undergraduate nursing education clinical experiences. Nurse Educ Pract 2014; 14: 271-4.
16. Tee S, Özçetin YSÜ, Russell-Westhead M. Workplace violence experienced by nursing students: A UK survey. Nurse Educ Today 2016; 41: 30-5.
17. Magnavita N, Heponiemi T. Workplace violence against nursing students and nurses: an Italian experience. J Nurs Scholarship 2011; 43: 203-10.
18. Amare TG, Tesfaye TT, Girmay B, Gebreagziabher TT. Exposure to occupational health hazards among nursing and midwifery students during clinical practice. Risk Manag Healthc Policy 2021; 14: 2211.
19. Attia NMN, Sorour AS, Ahmed FM. Occupational health hazards among faculty of nursing students in Zagazig University. Zagazig Nurs J 2018; 14: 133-47.
20. Al Qadire M, Ballad CAC, Al Omari O, et al. Prevalence, student nurses' knowledge and practices of needle stick injuries during clinical training: a cross-sectional survey. BMC Nurs 2021; 20: 187.
21. Veronesi L, Giudice L, Agodi A, et al. A multicentre study on epidemiology and prevention of needle stick injuries among students of nursing schools. Ann Ig 2018; 30: 99–110.
22. Suliman M, Al Qadire M, Alazzam M, Aloush S, Alsaraireh A, Alsaraireh FA. Students nurses' knowledge and prevalence of needle stick injury in Jordan. Nurse Educ Today 2018; 60: 23-7.
23. Unver V, Tastan S, Coskun H. The frequency and causes of occupational ınjuries among nursing students in turkey. Archives of Environmental & Occupational Health 2012; 67: 72-7.
24. Yang YH, Wu MT, Ho CK, et al. Needlestick/sharps injuries among vocational school nursing students in southern Taiwan. Am J Infect Contr 2004; 32: 431-5.

25. Prasuna J, Sharma R, Bhatt A, et al. Occurrence and knowledge about needle stick injury in nursing students. J Ayub Med Coll Abbottabad 2015; 27: 430-3.

26. Papadopoli R, Bianco A, Pepe D, Pileggi C, Pavia M. Sharps and needle-stick injuries among medical residents and healthcare professional students: pattern and reporting in Italy—a cross-sectional analytical study. Occup Environ Med 2019; 76: 739–45.

27. Souza-Borges FRF, Rıbeıro LA, Olıveıra LCM. Occupational exposures to body fluids and behaviors regarding their prevention and post-exposure among medical and nursing students at a Brazilian public university. Rev Inst Med Trop Sao Paulo 2014; 56: 157-63.

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Risk factors and maternal/fetal outcomes of pregnant women with abruptio placenta: a retrospective, descriptive study

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ABSTRACT

Aim: Abruptio placenta is one of the most important causes of antepartum bleeding and is linked to the major (unpleasant) obstetrics consequences leading to the increased risks of fetal and maternal morbidity and mortality. The aim of our study is to establish a prevalence in our tertiary hospital and find out the fetal and maternal outcomes, along with the patient's demographic characteristics and risk factors of abruptio placenta.

Material and Method: This trial was carried out in Profesör Doktor Cemil Taşçıoğlu State Hospital, between January 2018 and March 2022. Patient data were extracted from computer system, and files were retrospectively evaluated. We established the fetal and maternal outcomes, along with the demographic characteristics and risk factors of abruptio placenta. All analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 25.0, SPSS Inc., Chicago, IL, USA).

Results: Within the review period there were 7126 deliveries. And 112 cases with abruptio placenta were seen out of the total deliveries. In our population, prevalence of the abruptio placenta was calculated as 1.5%. Because of the incomplete data in certain files, only a total of 102 cases (91%) were eligible for the study.

Conclusion: In conclusion, since the abruptio placenta is highly associated with maternal and fetal morbidity and mortality, timely diagnosis is crucial to prevent devastating consequenuces.

Keywords: Abruptio placenta, risk factors, complications

INTRODUCTION

After the fetal viability and before the birth, partial or total detachment of a normally located placenta is called as abruptio placenta (1). The situation can be encountered in 0.5%–1% of pregnancies (2,3). It is one of the most important causes of antepartum bleeding and is linked to the major obstetrics consequences leading to the increased risks of fetal and maternal morbidity and mortality (4). Concealed or revealed types of hemorrhage may be seen in abruptio placenta. The concealed type is considerably hazardous due to the blood loss level does not correspond with maternal heart rate and blood pressure and is concluded to have more fetal death in comparison to the revealed type as well (5). Predisposing factors for abruptio placenta comprise hypertensive disorders of pregnancy, multiparity, being under the age of 20, advanced maternal age which is above 35, formerly having abruptio placenta, uterine anomalies, multiple pregnancy, polyhydramnios, smoking, cocaine use, blunt abdominal trauma, retroplacental leiomyoma, premature rupture of membranes, thrombophilic disorders, and short umbilical cord (4). The clinical signs depend on the degree of placental detachment and bleeding amount. Vaginal bleeding and abdominal pain are the most encountered presentation scenario. On the other hand uterine tenderness, preterm labor, hemodynamic instability, fetal distress, and fetal death may also be seen (2,5). The diagnosis is essentially clinical, although the sensitivity of ultrasound is low for diagnosis of abruptio placenta, it is useful for differential diagnosis for placenta previa (3,6). The low sensitivity of ultrasound is due to the fact that a retroplacental hematoma may be seen isoechoic relatively to the placenta on ultrasonography (7) The ultrasonographic view of abruptio placenta depends on the size, location, and the time period between the abruption and the ultrasonography (7). Diagnosis of abruptio placenta is almost always confirmed via direct

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visualisation of retroplacental clots at the separation site. Abruptio placenta should be evaluated and managed based upon the patient's clinical condition, blood loss level, fetal maturity and well being, whether the delivery starts or not, presence of any complication and the severity of placental abruption. In most of the cases decision comes out in favor of immediate delivery. The type of delivery is decided based upon the level of abruptio placenta, fetal well being, Bishop's score and severity of hemorrhage (8). Expe and far from term ctant management can be preferred in diligently selected cases with light bleeding, live fetus, reassuring cardiotocography (9). The aim of the expectant management is to help fetus get mature enough to survive. Some important maternal complications are antepartum hemorrhage, hypovolemic shock, pulmonary edema, disseminated intravascular coagulopathy, acute renal failure, and postpartum bleeding (2,10,11). Transfusions, if required, should include fresh whole blood, fresh frozen plasma, and cryoprecipitate (12). Emergency hysterectomy may be required in resistant postpartum bleeding. Abruptio placenta impose a high risk of fetal morbidity and mortality of which reasons are usually severe separation, misdiagnosis and delay in intervention (13,14).

In the light of all this, the aim of our study is to establish an incidence rate in our population based hospital and find out the fetal and maternal outcomes, along with the demographic characteristics and risk factors of abruptio placenta.

MATERIAL AND METHOD

The study was carried out with the permission of the Okmeydanı Training and Research Hospital Clinical Researches Ethics Committee (Date: 02.04.2019, Decision No: 1207) and informed consent was obtained from each participant. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This trial was carried on in a tertiary public hospital. 102 women with abruptio placenta were enrolled in the study that are confirmed during delivery between January 2018 and March 2022. Patient data were extracted from the computer system and files were retrospectively evaluated. Age, gravida, parity, gestational age, the clinical and sonographic findings at presentation, predisposing factors like hypertension, pre-eclampsia, eclampsia, polyhydramnios, early rupture of membranes, preterm labor, intrauterine growth restriction, smoking, blunt abdominal trauma and retroplacental leiomyoma, blood pressure, hemoglobin level, the gender of the fetus, birth weight, first- and fifth-minute Apgar scores, fetal demise, neonatal intensive care unit requirement are all obtained. At the same time, maternal complications such as disseminated intravascular coagulopathy, hypovolemic shock, acute kidney failure, presence of seizure, hysterectomy requirement, pulmonary edema, transfusion requirement, death were all recorded as well. Patients with complaints of vaginal bleeding and abdominal tenderness, along with ultrasonographic findings of retroplacental hematoma or collection and heterogeneity in placenta were prediagnosed as placental abruption. Definitive diagnosis was made by the direct visualization of retroplacental clots on the separated site during caeserean section or vaginal delivery. Chronic hypertension was determined as systolic blood pressure above 140 mmHg and diastolic pressure above 90 mmHg before the gestational age of 20 weeks or before the conception. Preeclampsia was described as systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg after the gestational age of 20 weeks with proteinuria (>300 mg/24 h or +1 by urine dipstick) or hypertension with thrombocytopenia, visual detoriation, pulmonary edema, increased serum creatinine levels, and abnormal liver and kidney function tests without proteinuria (15). Anemia is defined as having a hemoglobin (g/dL) value below 11 (acog ve anemi)??. Preterm labor was defined as labor between 24 and 37 gestational weeks whereas early preterm labor is accepted that occurring before 34 weeks of pregnancy. Rupture of membranes before the onset of labor was defined as early rupture of membranes; and the presence of regular contractions or cervical dilation before 37 weeks of pregnancy was termed as preterm labor (16). Education level of the patients was classsified into 3 subgroups: illiterate, education for 8 years or below and education period above 8 years. This is done since the compulsory schooling period in our country is 8 years.

All analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 25.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to evaluate the eligibility of the data for normal distribution. None of the variables did follow the normal distribution. So, descriptive statistical methods were used to evaluate frequency (n), percentage (%), and median (minimum-maximum) when appropriate.

RESULTS

During the review period there were 7126 deliveries. And 112 cases with abruptio placenta were seen out of the total deliveries submitting a prevalence of 1.5%. Because of the incomplete data in certain files, only a total of 102 cases (91%) were eligible. Median value with minimum and maximum values of patients' ages was 31.5 (19-42) years. Four cases (4%) were nulliparous, whereas 53 patients (51,9%) had parity of two or above. Median value with minimum and maximum values of patients' parities was

2 (0-4). Of all, 89 subjects (87.2%) were before term, while 13 (12.8%) presented at term. Among all, of the subjects, 85 (83,3%) cases had anemia. Eighteen subjects (17.6%) had an education period above 8 years whereas the rest (84 (82.4%)) had an education period of 8 or below. Forty three (42.1%) among all the cases were immigrants. Of all the cases, 49 subjects (48%) were unbooked with no antenatal recordings, they were referred from other hospitals. Dispersion of age, parity and education level data according to the subcategories is listed in **Table 1**. **Table 2** shows the risk factors of abruptio placenta. Hypertensive disorder of pregnancy was seen in 82 (80.3%) subjects. In all, 38 (37.2%) subjects were smokers. At the time of hospitalization, just 21 cases (11.7%) were in established labor. Majority of the complaints at presentation were vaginal bleeding along with abdominal pain as a second significant complaint. Fifteen cases (14.7%) were with early rupture of membranes. Most of the caesarean section decisions were made on account of abruptio placenta with live fetus. Twelve subjects (11.7%) had vaginal delivery whereas 90 (88.3%) had caesarean section. One (1%) subject was managed conservatively. Conservatively managed case went through caeserean section 24 hours after presentation. Twenty four (23.5%) subjects appeared to have concealed bleeding whereas 78 (76.5%) cases had revealed one. Maternal outcomes are depicted in **Table 3**. Of all, 2 (2%) maternal deaths were encountered. One patient having abruptio placenta was with subplacental leiomyoma and hypovolemic shock and was one of the two maternal losses in this study. Other maternal death had resulted from the hypovolemic shock led by abruption after a traffic accident. In all, 51 (50%) subjects had hypertensive disorders. Fourty four (43.1%) subjects received blood transfusion due to heavy bleeding. Twenty four (27%) of those that had caesarean section were with a Couvelaire uterus. Neonatal outcomes are depicted in **Table 4**. There were 89 live births (87.3%) and 13 still births (12.7%). Median value of fetal birth weight and gestation age were 2600 (880-3100) and 34 (28-38), respectively. The number of the subjects with an Apgar score below 7 at first-minute and at fifth minute were 73 (71.6), and 48 (47.1%), respectively. In 13 (12.7%) of the subjects, the first-minute Apgar score was noted as "0." Fifty seven (55.9%) fetuses were male. Among stillbirths, 10 (77%) fetuses were male. Fourty one (40%) fetuses were admitted to the neonatal intensive care unit just after delivery.

DISCUSSION

Abruptio placenta is one of the most dangerous complications of pregnancy, since it has poor outcomes for the mother and the child. In our study the incidence of abruptio placenta was 1.5%. This value is slightly higher than the 0.5-1.1% rate of incidences observed in West and Asian populations (4,17-19). The higher incidence of AP in our study may be due to the fact that our hospital is a tertiary referral public hospital with its high patient capacity. Some observational studies have concluded that the levels of vitamin A, b-carotene, and vitamin E in peripheral venous blood of women with abruptio placenta. In our study 43 (42.1%) patients were immigrants, 84 subjects (82.4%) had an education period of 8 or below and 85 (83.3%) patients had anemia, however it could not be concluded if the anemia was the cause or consequence, of antepartum hemorrhage, since many patients were unbooked (49(48%)) with no antenatal records. We suppose that the high frequency of maternal anemia is a result of both the bleeding of abruption and maternal nutritional deficits commonly prevalent in immigrants and populations with low socioeconomic strata.

Table 1. Sociodemographic characteristics along with subcategories

	Frequency (n)	Percentage (%)
Age		
≤19	2	2
20-29	43	42.2
30-39	49	48
≥40	8	7.8
Parity		
0	4	4
1	45	44.1
2	34	33.3
3	14	13.7
4	5	4.9
Education level		
Illiterate	10	9.8
≤8 years education	74	72.6
>8 years education	18	17.6

Table 2. Risk factors for abruptio placenta

	Frequency (n)	Percentage (%)
Hypertensive disorders	82	80.3
Trauma	1	1.4
Subplacental leiomyoma	1	1.4
Smoker	38	37.2
Short cord	1	1.4
Preterm birth	12	16.9
Multiparity	53	51.9

Table 3. Maternal Complications

	Frequency (n)	Percentage (%)
Blood transfusion	44	43.1
Postpartum haemorrhage	14	13.7
Acute renal failure	5	4.9
Disseminated intravascular coagulation	16	15.6
Caesarean hysterectomy	4	3.9
Ligation of internal iliac or uterine arteries	8	7.8
Maternal mortlity	2	2
Hypovolemic shock	3	2.9
Couvelaire uterus	24	23.5

Table 4. Neonatal outcomes	
Gestational age in years (Median (min-max))	**34 (28-38)**
Birth weight (Median (min-max))	2600 (880-3100)
Gender	
Female (n (%))	45 (44.1)
Male (n (%)	57 (55.9)
First minute APGAR score (Median (min-max))	5 (0-8)
Fifth minute APGAR score (Median (min-max))	7 (0-10)
Stillbirth (n (%))	13 (12.7)
Neonatal intensive care unit admission (n (%))	41 (40)

High parity and advanced maternal age are accepted as well-known risk factors for abruptio placenta (6, 20-23). In our study 51% of patients had parity of two and above. This rate is not consistent with the result of 80% in Adalı et al.'s (24) article. On the other hand, rates of maternal age above 30 of our study and Adalı et al.'s article were 57% and 46%, respectively.

The association of abruptio placenta with hypertension was demonstrated in some studies (10,11,13). In our study 80,3% of the subjects had hypertensive disorders. In our country, in two studies, this rate is reported as 30% and 53,3% which are not consistent with ours (24,25). The reason of this discrepancy may be due to the fact that significant number of the subjects in our study were unbooked and our hospital is a tertiary center where referred patients are accepted. Lack of appropriate antenatal care and low socioeconomic status are linked with unfortunate medical conditions like hypertension in pregnancy (26).

In this study it it is documented that majority (88.3%) of the subjets were delivered by emergency caesarean sections. This is similar to a study conducted by Cakmak et al. (27). However, some other studies revealed a larger proportion of patients having vaginal delivery (14). This disparity may depend on the fetal well being at presentation. And in our study there were only 21 cases (11,7%) in established labor. Since the time from presentation to the birth has a big impact on fetal well being, emergency caeesarean section may be the prompt choise for practitioners. The best menagement for abruptio placenta with a live fetus is caesarean section (2).

Preterm labor and early rupture of membranes are also risk factors for placental abruption. In our study there were 15 (14.7%) subjects presented with early rupture of membranes. This rate is consistent with some other studies which have a range between 8 and 16% (17,26,27).

The risk of placental detachment after trauma is 2% which should be carefully taken into account (26,28). In this study, we observd only one case (1%) of abruptio placenta with a history of trauma. American Colleage of Obstetricians and Gynecologists recommends a minimum of 4-hour surveillance for the pregnant women after abdominal trauma (29). We, in our practice, accept the pregnant women with a history of trauma as inpatient for at least 24 hours.

It is noteworthy that only one patient (1%) was managed conservatively. This is an exception since abruptio placenta is an obstetric emergency. Early onset severe preeclampsia, requires delivery of the fetus at a very preterm gestation in order to prevent severe maternal complications. This may cause poor perinatal outcomes. The complications of iatrogenic premature birth are more common in low resource settings. Expectant management of severe preeclampsia, far from term, therefore may be necessary to prevent such detrimental events in the fetus. But expectant management may result in fetal loss or fetal asphyxia (9,30)

Abruptio placenta is also associated with high perinatal mortality and morbidity. It has been concluded that 12% of all perinatal deaths is due to abruptio placenta (2). In our study, there were 13 (12.7%) perinatal deaths. This is consistent with the results in some other studies carried on in other tertiary hospitals (2,22). The high perinatal mortality rates highlight the importance of immediate intervention. During pregnancy, intrapartum and postpartum periods disseminated intravascular coagulation rate is about 35%, and it is more encountered among placental abruption cases (31). Furthermore, in placental abruption subjects, the rates of maternal loss, hysterectomy, pulmonary edema, disseminated intravascular coagulation and renal failure were revealed to be high especially due to hypertensive disorders (26). In our study there were 44 (43.1%) cases that had blood transfusion which is consistent with some other studies (18,27). In 20-30% of cases vaginal bleeding can be absent when hemorrhage is concealed in the uterus (5,32). Therefore, the observed amount of bleeding is useless to estimate the accurate loss from the maternal circulation. In our study 24 (23.5%) subjects were with concealed hemorrhage which is consistent with the literature.

The two maternal deaths in our study were both unbooked patients with no antenatal surveillance in our department. Both cases were found to be presented late to the hospital with irreversible shock with massive hemorrhage. This highlights the importance of early presentation and immediate management to refrain from the adverse maternal and fetal outcomes of abruptio placenta.

There is an association between placental abruption and preterm labor, low birth weight, fetal demise (8). The perinatal mortality and morbidity of placental

abruption is dependent on the amount of placenta separated and the gestational week. Stillbirth rate is considerably high when the seperation percentage is over 50% relative to the whole placental bed (33). In abruptio placenta the rate of perinatal death secondary to the preterm birth is reported with a range of 36-59% (2,11). In a Turkish study mean gestational week and birth weight are found as 31,36 weeks and 2153 gram, respectively (24). In another Turkish study, mean gestational age and mean birth weight are reported as 28,25 weeks and 1988 grams, respectively (26). In our study, median gestational age was 34 (28-38) weeks and median birth weight was 2600 (880-3100) grams. In abruptio placenta, neonatal asphyxia and death rate tend to be high. Furthermore, APGAR scores of the neonates have a tendency to be lower in patients with abruptio placenta. Adalı et al. (24) reported the first and fifth minute APGAR score mean values as 2 and 2,9, respectively. On the contrary, we found the same scores in median values as 5(0-8) and 7 (0-10), respectively. The reason of the discrepancies between studies, is that stillbirth rate was 12.7% in our study whereas the same rate was 61% in Adalı et al. (24) article. Moreover there is one report concluding that if the fetus is male, the risk of abruptio placenta is higher (34). In our study, of all fetuses there were 57 (55.9%) male fetuses and among 13 stillbirths, 9 (70%) were male.

CONCLUSION

Since the abruptio placenta is highly associated with maternal and fetal morbidity and mortality, timely diagnosis is crucial to prevent devastating consequencies. In pregnant women presenting with vaginal bleeding, pain and even if the ultrasonographic examination is normal placental abruption should still be kept in mind in differential diagnosis. Antenatal care which reveals the risk factors like hypertensive disorders has a big role in preventing the abruptio placenta and alleviating the maternal and fetal outcome.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Okmeydanı Training and Research Hospital Clinical Researches Ethics Committee (Date: 02.04.2019, Decision No: 1207).

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. Fernandes J, Gopalakrishna N. Maternal and fetal outcome in abruptio placentae at a tertiary care centre: a retrospective analysis. Int J Reproduct Contracept Obstet Gynecol 2021; 10: 3860-3.
2. Ananth CV, Wilcox AJ. Placental abruption and perinatal mortality in the United States. Am J Epidemiol 2001; 153: 332-7.
3. Janakiram P, Sellathamry SG, Ponnivalavan K. Maternal and perinatal outcome in abruptio placenta. J Evid Based Med Healthc 2017; 4: 3985-8.
4. Khan S, Chughani G, Amir F, Bano K. Frequency of abruptio placenta in women with pregnancy-induced hypertension. Cureus 2022; 14: e21524.
5. Oyelese Y, Ananth CV. Placental abruption. Obstet Gynecol 2006; 108: 1005-16.
6. Bibi S, Ghaffar S, Pir MA, Yousfani S. Risk factors and clinical outcome of placental abruption: a retrospective analysis. J Pak Med Assoc 2009; 59: 672-4.
7. Shinde GR, Vaswani BP, Patange RP, Laddad MM, Bhosale RB. Diagnostic performance of ultrasonography for detection of abruption and its clinical correlation and maternal and foetal outcome. J Clin Diagn Res 2016; 10:4-7.
8. Qiu Y, Wu L, Xiao Y, Zhang X. Clinical analysis and classification of placental abruption. J Matern Fetal Neonatal Med 2021; 34: 2952-6.
9. Bond AL, Edershim TG, Curry L, Druzin ML, Hotson JM. Expectant management of abruptio placentae before 35 weeks gestation. Am J Perinatol 1989; 6: 121-3.
10. Anantt CV, Peltier MR, Kinzler WL, Smulian JC, Vintzileos AM. Chronic hypertension and risk of placental abruption: Is the association modified by ischemic placental disease? Am J Obstet Gynecol 2007; 197: 273.e1-7.
11. Tikkanen M. Placental abruption: epidemiology, risk factors and consequences. Acta Obstet Gynecol Scand 2011; 90: 140-9.
12. Arnold DL, Williams MA, Miller RS, Qui C, Sorensen TK. Iron deficiency anaemia, cigarette smoking and risk of abruptio placentae. J Obstet Gynaecol Res 2009; 35: 446-52.
13. Abdella TN, Sibai BM, Hays JM Jr, Anderson GD. Relationship of hypertensive disease to abruptio placentae. Obstet Gynaecol 1984; 63: 365-70.
14. Abasi IJ, Jeremiah I, Ekine AA. Risk factors and pregnancy outcome of placental abruption at the Niger Delta University Teaching Hospital, Okolobiri, South-South Nigeria. Br J Med Med Res 2015; 5: 1000-6.
15. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122: 1122–31.
16. Menon R, Fortunato SJ. Infection and the role of inflammation in preterm premature rupture of the membranes. Best Pract Res Clin Obstet Gynaecol 2007; 21: 467-78.
17. Pariente G, Wiznitzer A, Sergienko R, Mazor M, Holcberg G, Sheiner E. Placental abruption: critical analysis of risk factors and perinatal outcomes. J Matern Fetal Neonatal Med 2011; 24: 698-702.

18. Ananth CV, Oyelese Y, Yeo L, Pradhan A, Vintzileos AM. Placental abruption in the United States, 1979 through 2001: Temporal trends and potential determinants. Am J Obstet Gynecol 2005; 192: 191-8.
19. Rasmussen S, Irgens LM, Bergsjo P, Dalaker K. The occurrence of placental abruption in Norway 1967-1991. Acta Obstet Gynecol Scand 1999; 75: 222-8.
20. Hung TH, Hsieh CC, Hsu JJ, Lo LM, Chiu TH, Hsieh TT. Risk factors for placental abruption in an Asian population. Reprod Sci 2007; 14: 59-65.
21. Daffalah SE, Babikir HE. Risk factors predisposing to abruptio placentae. Maternal and fetal outcome. Saudi Med J 2004; 25: 1237-40.
22. Musau H, Sagay AS, Ekwempu CC, Ibrahim SA. Analysis of some risk factors for abruptio placentae in Jos, Northern Nigeria. Trop J Obstet Gynaecol 2007; 24: 11-4.
23. Takai IU, Sayyadi BM, Galadanci HS. Antepartum hemorrhage: a retrospective analysis from a Northern Nigerian Teaching Hospital. Int J Appl Basic Med Res 2017; 7: 112-6.
24. Adalı E, Yıldızhan R, Kolusarı A, et al. Dekolman plasenta olgularının retrospektif değerlendirilmesi. Van Med J 2009; 16: 14–8.
25. Ulkumen BA, Pala HG, Calık E, Koyuncu FM. Ablasyo plasenta olgularının retrospektif olarak değerlendirilmesi. DEU Tıp Fakultesi Dergisi 2014; 28: 15–9.
26. Yılmaz M, İsaoğlu U, Delibaş İB, Uluğ P, İngec M, Al RA. Dekolman plasenta: epidemiyoloji, risk faktorlerinin analizi, fetal ve maternal sonuclar. Sakarya MJ 2013; 3: 126–30.
27. Cakmak BD, Turker UA, Dundar B, Yumru AE, The retrospective analysis of abruptio placenta cases in a tertiary center: risk factors and perinatal outcomes. Haydarpasa Numune Med J 2019; 59: 88–94
28. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Obstetrical hemorrhage. In: Williams obstetrics. 23rd ed. New York: Mc Graw-Hill; 2010. p. 527-47.
29. ACOG educational bulletin. Obstetric aspects of trauma management. Number 251, September 1998 (replaces Number 151, January 1991, and Number 161, November 1991). American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 1999; 64: 87–94.
30. Churchill D, Duley L, Thornton JG, Jones L. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. The Cochrane Database of Systematic Reviews 2013; 7: CD003106.
31. Konje JC, Taylor DJ. Bleeding in late pregnancy. In: James DK, Steer PJ, Weiner CP, Gonik B (eds). High risk pregnancy, 3rd edn. Edinburgh, UK: WB Saunders: 2006.
32. Hall DR. Abruptio placentae and disseminated ıntravascular coagulopathy. In. Seminars in perinatology. WB Saunders, 2009; 33: p 189-95.
33. Hladky K, Yankowitz J, Hansen WF. Placental abruption. Obstet Gynecol Surv 2002; 57: 299–305.
34. Aliyu MH, Salihu HM, Lynch O, Alio AP, Marty PJ. Placental abruption, offspring sex, and birth outcomes in a large cohort of mothers. J Matern Fetal Neonatal Med 2012; 25: 248–52.

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Comparison of non-invasive imaging methods and laboratory findings on non-alcoholic fatty liver disease (NAFLD) in childhood

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ABSTRACT

Aim: Diagnosis and follow-up of non-alcoholic fatty liver disease in children with practical and non-invasive methods have been researched for many years. Ultrasonography (USG), Shear wave elastography (SWE), and Magnetic Resonance (MR) are thought to help demonstrate the impairment which is also displayed in liver function tests. This study aims to identify the most effective imaging method among liver scanning methods in exhibiting the fatty condition of the liver and laboratory tests.

Material and Method: This study was carried out on a population of 84 children who applied to the clinic. The relationship between the diagnostic performances of three different noninvasive methods [USG, MR, and SWE] and liver function tests in children with suspected NAFLD was analyzed. Age, BMI (body mass index), waist circumference, gender, liver function tests, total cholesterol, triglyceride, and Homeostasis Model Assesment-Insulin Rezistance (HOMA-IR) parameters of NAFLD and control group were put into comparison and their relationship with USG, MR, and SWE imaging methods were also analyzed.

Results: There is no statistically significant relationship between hepatosteatosis grade and the mean SWE ($p>0.05$) while there is a positive and statistically significant relationship between waist circumference and liver long axis values at 33.3% level ($p: 0.036$; $p<0.05$). On the other hand, there is no statistically significant difference in laboratory values between those with and without NAFLD based on MR and SWE examinations ($p>0.05$).

Conclusion: Abdominal USG, SWE, and dynamic MR examinations are very essential to demonstrate liver functions and liver pathology in children with non-invasive methods. It is also useful in patient follow-up. In this study, no difference was detected between SWE and MR findings, and we think that the SWE examination will be more suitable in estimating liver functions in follow-up as opposed to costly MR examination.

Keywords: Fatty liver disease, elastography, scanning method, ultrasound

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) can range from simple steatosis to non-alcoholic steatohepatitis (NASH); it is an illness that can lead to cirrhosis and liver failure as a result of the progression of fibrosis (1). NAFLD is the most common chronic liver disease in the world today. There is a marked increased risk of cardiovascular mortality in NAFLD (especially in the more severe form of NASH) (2). The clinical significance of fatty liver disease is increasingly better understood. Especially in the last two decades, many scientists have focused on distinguishing the subtypes of this disease. Because, unlike simple steatosis, NASH is a progressive form of the disease. Although it is now accepted that simple steatosis and NASH are two histological subtypes of the NAFLD spectrum, these two conditions are probably completely different not only in terms of clinical results but also in terms of histological and pathophysiology (3). Fibrosis is not expected to accompany simple steatosis. NASH can be accompanied by fibrosis and cause cirrhosis. Advanced stage fibrosis is detected in 20% of patients with NASH, and this is directly related to the prognosis of the disease (4). Therefore, it is recommended to consider these issues in noninvasive diagnostic studies.

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Liver biopsy is considered to be the gold standard in distinguishing simple steatosis from NASH in patients with NAFLD. However, it is an invasive procedure that may have serious clinical complications and it is not easily accepted by the parents of pediatric patients. It is highly ineffective for follow-up and unsuitable for a large screening of patients at risk (such as obesity, type 2 DM, hyperlipidemia). Due to the increasing prevalence of obesity and diabetes, economic, simple, and easily accessible screening tests are required instead of costly, invasive, and specialized methods. Furthermore, insufficient material, sampling errors, and human mistake may be a problem in the pathological examination. Therefore, a non-invasive method is needed. Besides, there is no single ideal method for NAFLD. Moreover, the use of models (panels) or scoring systems belonging to different pathophysiological mechanisms can raise diagnostic accuracy (5).

Our objective in this study is to compare the diagnostic performances of 3 different noninvasive methods [USG, MR, and SWE] in the analysis of liver functions in individuals with NAFLD. SWE is an ultrasonic medical device that predicts fibrosis by measuring liver stiffness with the help of a sort of elastic wave (6). Until now, studies adopting USG, MR, and SWE together in the Turkish population are limited. In many patients with suspected NAFLD, the reliable detection of fibrosis by only taking blood and/or performing SWE without the need for an invasive procedure in outpatient and clinical conditions can help us identify patients who need a liver biopsy.

MATERIAL AND METHOD

The study was carried out with the permission of Taksim Training and Research Hospital Ethics Committee (Date: 26/06/2019, Decision No: 81). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

The patients, or their parents or guardians, signed written statements of informed consent. Included in this study were obese patients who applied to Gaziosmanpaşa Training and Research Hospital and diagnosed with NAFLD, and a control group consisting of children with similar age and gender.

Patients with viral hepatitis, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary stenosis, alpha-1 antitrypsin deficiency, myocarditis/myopathy, congenital heart disease, cerebrovascular disease, and malignancy were excluded from the study. Moreover; patients with a history of drug use that may cause NAFLD (such as anti-epileptic drugs), patients on insulin therapy for diabetes, those with iron deficiency anemia or acute severe inflammatory disease, and those with rheumatological and autoinflammatory diseases were also left out.

Clinical and Biochemical Analysis

Physical examination, anthropometric and biochemical measurements were performed on all cases. Blood samples were taken from all patients in the study who fasted overnight. Serum samples were taken from patients, before the study and adjusted according to the quantities to be used once for each ELISA test. Patients' liver function tests (ALT, AST, albumin, GGT), serum lipid profile (triglyceride, LDL, HDL), insulin, and fasting blood glucose were measured and HOMA-IR was calculated.

Abdominal USG and Shear wave Elastography (SWE)

Abdominal USG was performed on the patients following a fasting period of 6 hours. Since ultrasound is among the first preferred medical imaging methods.

The diagnosis of liver steatosis was made based on increased echogenicity of the liver parenchyma compared to the right renal cortex in USG. Visibility and sharpness of the diaphragm and hepatic vessel walls were also analyzed. Based on these 3 parameters, steatosis was classified into 3 distinct grades: Grade 0, no steatosis (liver and renal cortex with the same echogenicity); Grade 1, mild steatosis: liver slightly more echogenic than the renal cortex, clear visualization of the diaphragm, and sharply contoured hepatic veins; Grade 2, moderate steatosis: more echogenic liver and diaphragm while hepatic veins still being visible with debilitated USG beam in the deeper parts of the liver, albeit with blunt contours; Grade 3, severe steatosis: advanced echogenic liver, severe USG beam attenuation, neither diaphragm nor hepatic veins visible (7).

SWE values of all NAFLD patient groups were measured with fibroscan instrument using suitable probes on the patients. Shear Wave Elastography method is used on the liver. SWE results of the patients were obtained by examining their existing records. The fact that at least 10 valid measurements were taken from the patients was accepted as a reliable measurement. During and just prior the measurements, the patient was requested neither to breathe nor to take a deep breath.

Dynamic Magnetic Resonance Imaging

MR imaging was performed with a 1.5-T device (Intera, software version 8.1; Philips Medical Systems, Eindhoven, The Netherlands) using a phased-array

coil. Multi-stage contrast-enhanced dynamic series were obtained just before and after intravenous rapid bolus administration of 0.1 mmol of gadopentetate dimeglumine per kilogram body weight to patients while in the magnetic cylinder. Imaging timings of the dynamic series included precontrast, arterial, portal and stabilization phases. Processing of multiphase, contrast, dynamic images was done automatically by the MR imaging device. The software that was used made it possible to extract precontrast images separately from those images taken during arterial, portal, and equilibration stages on each patient.

Statistical Analysis

IBM SPSS Statistics 22 software package was used for evaluating the findings of the study. The normality assumption of the parameters was checked with Shapiro-Wilks test. While evaluating the study data, besides descriptive statistical methods (mean, standard deviation, frequency), Student t-test was used for comparing normally distributed parameters between two groups, whereas Mann Whitney U test was deployed for comparisons of non-normally distributed parameters between two groups. Fisher Freeman Halton test and Continuity (Yates) Correction were used for comparing qualitative data. Pearson correlation analysis was used to examine the relationships between parameters that are suitable for normal distribution, and Spearman's rho correlation analysis was used to examine the relationships between parameters not compatible with normal distribution. Significance was checked at the p <0.05 level.

RESULTS

The study was conducted between 2018 and 2019 with a total of 84 children, 55 (65.5%) girls and 29 (34.5%) boys, aged between 4 and 17. The average age of the children is 12.23±3.47. The study was examined under 2 groups, 40 of which are NAFLD (47.6%) and 44 (52.4%) as control. NAFLD and the control group were similar in age and gender. The liver function tests ALT and GGT were higher in the NAFLD group than in the control group (**Table 1**). 35% of the patients in the NAFLD group had Grade 1 hepatosteatosis while 55% of them had Grade 2 and 10% Grade 3 hepatosteatosis, respectively. Liver long axis values and elastography average were significantly higher than the control group (p:0.000; p<0.05). Hemoglobin and insulin levels of the NAFLD group were significantly higher than the control group (p: 0.006; p<0.05). HDL level was found to be low in the NAFLD group as expected (**Table 2**). There is no statistically significant difference between the groups in terms of LDL and blood glucose levels (p>0.05) (**Table 2**).

Table 1. Evaluation of age, BMI, waist circumference, gender, ALT, AST, GGT, albumin, total cholesterol, triglyceride, and HOMA-IR parameters among the groups

	NAFLD group	Control group	p
	Mean±SD	Mean±SD	
Gender n (%)			0.216[2]
Female	23 (57.5%)	32 (72.7%)	
Male	17 (42.5%)	12 (27.3%)	
Age	13.33±2.62	12.23±3.85	0.09*[1]
BMI	28.63±5.81	24.45±3.48	0.000*[1]
Waist circumference	94.51±13.06	68.41±6.91	0.000*[1]
ALT (median)	61.53±86.04 (34.5)	18.32±8.34 (16)	0.000*[3]
AST (median)	42.58±37.73 (30)	28.34±9.09 (26.5)	0.137[3]
GGT (median)	31.08±20.38 (24)	15.48±9.06 (12)	0.000*[3]
Albumin (median)	4.42±0.36 (4.5)	4.44±0.32 (4.5)	0.728[3]
Total cholestrol	169.58±38.05	162.52±34.55	0.376[1]
Trigliserid (median)	138.65±77.17 (120.5)	139.09±48.13 (147)	0.237[3]
HOMA-IR (median)	4.03±2.31 (3.4)	2.48±0.69 (2.4)	0.000*[3]

[1]Student t test, [2]Continuity (yates) correction, [3]Mann Whitney U test, *p<0.05

Table 2. Evaluation of liver long axis, liver elasto average, hepatosteatosis grade, MR, Hb, LDL, HDL, insulin and blood glucose parameters among the groups

	NAFLD group	Control group	p
	Mean±SD	Mean±SD	
Liver long axis	147.13±11.85	120.7±15.99	0.000*[1]
Liver elasto avg (median)	1.79±0.30 (1.7)	1.6±0.15 (1.6)	0.000*[2]
Hepatosteatosis n(%)			0.000*[3]
None	0	44 (100%)	
Grade 1	14 (35%)	0 (0%)	
Grade 2	22 (55%)	0 (0%)	
Grade 3	4 (10%)	0 (0%)	
MR n(%)			0.000*[4]
No	15 (37.5%)	44 (100%)	
Yes	25 (62.5%)	0 (0%)	
Hb	13.12±0.88	12.49±1.15	0.006*[1]
LDL(median)	104.03±39.66 (104.5)	104.16±27.67 (102)	0.854[2]
HDL	43.5±8.61	49.86±9.39	0.002*[1]
Insulin(median)	19±10.22 (15.7)	11.07±2.39 (11)	0.000*[2]
Blood glucose	87.85±8.09	90.11±11.4	0.301[1]

[1]Student t test, [2]Mann Whitney U test, [3]Fisher Freeman Halton test, [4]Continuity (yates) correction, *p<0.05

62.5% of the patients who were diagnosed with NAFLD based on the USG actually presented NAFLD in MR results. There is a positive and statistically significant correlation between the degree of hepatosteatosis and liver long axis values at 48.1% level (p: 0.002; p<0.05). On the other hand, there is no statistically significant correlation between liver elasto average and hepatosteatosis (p>0.05).

There is a positive, and statistically significant correlation between waist circumference and liver long axis values (p: 0.036; p<0.05). There is no statistically significant relationship between the mean liver elasto and waist circumference (p>0.05) (**Table 3**).

Table 3. Evaluation of the correlation between hepatosteatosis and waist circumference and liver long axis and liver elasto values in the patient group

	Hepatosteatosis	Waist circumference
Liver long axis		
r	0.481	0.333
p	0.002*	0.036*
Liver elasto avg		
r	0.114	-0.007
P	0.485⁺	0.964

Pearson correlation analysis, ⁺Spearman Rho correlation analysis, *p<0.05

DISCUSSION

NAFLD is closely associated with obesity and is generally accepted as the liver component of metabolic syndrome. The frequency of NAFLD continues to increase in the population. In this study, BMI mean value in children with NAFLD is 28.63±5.81 kg/m². Similarly, in a study on NAFLD in children in Malaysia, the BMI average was 29.8 kg/m² (8). Although Asians have a similar BMI to Caucasians, they develop complications associated with obesity and diabetes at a lower BMI than their Western peers due to higher visceral fat accumulation in Asia (9). Although these milestone studies were primarily conducted in adults, the conclusion that Asian children had more visceral steatosis compared to western population of the same body mass index was considered as an outcome of similar studies in the pediatric population.

For NAFLD patients, it is not only common to have high BMIs, but also other parameters of metabolic syndrome at high levels (i.e., fasting blood glucose, HOMA-IR, and hypercholesterolemia) (10). In a study on adults, 60.4% of NAFLD patients diagnosed with USG were Grade 1, 33.6% Grade 2, and 5.9% Grade 3 according to the degree of liver steatosis. In these groups, blood glucose, HOMA-IR, and serum lipid values (triglyceride, LDL) rose as the USG grade increased (11). In this study, 35% of the patients in the NAFLD group had Grade 1, 55% had Grade 2, and 10% had Grade 3 hepatosteatosis, respectively. Since the number of patients in these sub-groups was insufficient, a general comparison between the patient and the control groups instead was made. Insulin levels of the NAFLD group were found to be significantly higher than the control group (p<0.05). HDL levels were also found to be significantly lower in NAFLD patients as expected in comparison to the control group (p:0.002; p<0.05). A study conducted in China indicated that increased serum HbA1c level was significantly associated with NAFLD risk. The risk is explained by two mechanisms: the HbA1c level being affected by the lifetime of erythrocytes and the "glucose permeability". Insulin resistance in NAFLD leads to an increase in hepatic glucose production and an increase in serum glucose level and hence, HbA1c in the blood. In NAFLD, it causes oxidative stress which causes changes in erythrocyte morphology by reducing the membrane fluidity of erythrocytes and facilitates its capture by liver macrophage. This increased erythrocyte destruction also increases HbA1c (12). Studies on lipid profile have shown that high triglyceride and LDL levels were the only factors that exhibited a significant relationship with the degree of liver inflammation. The inclusion of such lipid abnormalities in the etiology of NAFLD in non-diabetic patients, was found to be a significant contribution of increased BMI, triglyceride and reduced HDL in the development of NAFLD (13). In our study, however, there was no significant difference between the children with NAFLD and the control group in terms of LDL and blood glucose levels (p>0.05).

There was no statistically significant difference between the patients with NAFLD and the control group in terms of the levels of AST, albumin, total cholesterol, triglyceride parameters (p>0.05). In a cohort study carried out by Adams et al. (14) in Minnesota in 2005, biochemical parameters of NAFLD patients were not found to be statistically different from individuals in the general population. However, in this group, NAFLD ranks 13th among all causes of death in the general population, and 3rd among causes of death due to liver diseases. NAFLD is the most common cause of chronic liver disease in the United States of America (USA) (15). While the average prevalence of NAFLD in the community is 20-30%, that of NASH is around 3.5-5%. NAFLD can be seen in every gender, race and age group, including children (16). According to the estimates of the World Health Organization (WHO), more than 20 million people are expected to develop cirrhosis due to NAFLD in the coming decades, and NAFLD is expected to be the most common cause of liver transplantation in 2023 (17). Because it is such a widespread public health problem, it is evident that governments and healthcare organizations need to take measures and raise awareness for this simple but mortal disease of the liver. In another study, liver-related mortality rate was found to be 1.7% in 420 NAFLD patients who were followed up for 7 years. Hepatocellular carcinoma developed in 2 patients whereas liver transplantation was required for 1 patient. In the study, advanced age, impaired glucose tolerance and cirrhosis were associated with higher mortality risk (18).

In this study, the liver long axis values and the mean SWE of the patient group were significantly higher than those of the control group (p: 0.000; p<0.05). In the study by Makkonen et al. (19), alcohol consumption, regular drug use, and monozygotic and dizygotic twins (n=313) without chronic liver disease were analyzed. It was observed that SWE values rose as the liver size increased in these patients. The relationship between serum ALT, fasting insulin levels and fatty liver was also investigated in the study. In both monozygotic and dizygotic twins, a strong association of high serum ALT and fasting insulin levels and liver fat content was found out. In our study, the mean age, BMI, mean waist circumference, ALT, GGT, HOMA-IR levels of the patient group were found to be significantly higher than the control group (p<0.05). In a study conducted in Malaysia, it was displayed that BMI was significantly higher in patients with steatosis compared to patients without steatosis (p=0.003). Metabolic parameters and HOMA-IR were significantly associated with fibrosis in patients with fibrosis (p<0.05). Fibrosis is three times more likely to occur in the presence of metabolic syndrome. Abdominal obesity causes a decrease in insulin sensitivity, as visceral adipose tissue is highly resistant to insulin and sensitive to lipolysis, it produces more free fatty acid than adipose tissue in other regions (20,21). The greater availability of substrate for lipogenesis, together with the relative hyperinsulinemia effect, increases hepatic lipogenesis, which leads to a vicious circle (22). This study highlighted no statistically significant difference between the groups in terms of AST, albumin, total cholesterol, triglyceride parameters levels (p>0.05). In a study conducted by Pacifico et al. (23), it was shown that insulin resistance and triglyceride: HDL-C ratio had a significant relationship with liver fibrosis in the presence of other metabolic parameters, and it was thought to explain its key role in the pathogenesis of NAFLD. In our study, there was no statistically significant difference between the children with NAFLD and the control group in terms of LDL and blood glucose levels (p>0.05).However, a study on adults highlighted a difference between LDL and blood sugar levels between NAFLD patients and the control group. In addition, liver elastography results of NAFLD patients were found to be higher than the control group (24).

There is a positive and statistically significant relationship between waist circumference and liver long axis values with a correlation coefficient of 33.3%. Waist circumference is an important indicator of central obesity and visceral fat. The decrease in body mass index with the lifestyle change of the patients, namely dietary modification and physical activity-enhancing change is the basis of real therapeutic recommendations for NAFLD. A loss of 7% in initial body mass significantly improves liver function. (25). A meta-analysis of 78 studies (38 NASH studies and 40 NAFLD studies, including liver biopsy studies) showed that a 5% reduction in baseline body weight contributed to a reduction in histological liver steatosis, but not fibrosis. A loss of 7% of initial body weight significantly improved the histological structure of the liver (p: 0.036; p<0.05). In our study, there was no statistically significant relationship between waist circumference and average SWE (p>0.05). In this case, it supports the fact that liver fibrosis is not affected (26). However, a significant relationship was noted in other studies abroad. Guidelines for non-invasive evaluation of liver disease in the adult population have been developed and these guidelines should be validated on children (27).

Based on MR results, ALT values in NAFLD patients were higher than the control group while AST values were similar between the two groups (p<0.05). However, ALT and AST values may not always reflect the state of the liver. Although elevated aminotransferase levels are common in most patients, their normalness does not exclude steatohepatitis and fibrosis. In a study carried out by Mofrad et al. (28), 51 patients with normal ALT levels were examined and bridging fibrosis was observed in 12 of them and cirrhosis was prevalent in 6 of the subjects.

There are several limitations to our study. Firstly, our sample size is relatively small and consists only of Turkish population. Secondly, the number of severe NAFLD cases in our patient population is very low. In this study, instead of finding the diagnostic performance of these three different noninvasive diagnostic methods (USG, SWE and MR), we analyzed the diagnostic performance of NAFLD groups in determining the relationship between liver function tests. The main reason for this was that we did not have enough patients for each NAFLD stage. Moreover, liver biopsy was not performed on NAFLD patients since it is invasive and it has no definite indication.

CONCLUSION

Abdominal US, SWE and MR examinations in analyzimg liver functions and NAFLD status were compared based on their effectiveness. It is highly essential to demonstrate liver functions and liver pathology in children with non-invasive methods. It is also useful in patient follow-up. In this study, no difference has been detected between SWE and MR findings, and we are of the opinion that SWE examination will be more practical in estimating liver functions in patient follow-up since MR examination is more costly.

NAFLD continues to be an increasingly common public health problem in children. It is important for patients to follow counseling from specialized dieticians, pediatric gastroenterologists and pediatric endocrinologists and of course, proper follow-up is also crucial. During this follow-up, imaging tools and tests that enable non-invasive evaluation of the liver would be very valuable.

We are of the opinion that body measurements, especially waist circumference, metabolic parameters and advanced US methods (SWE, TE) are highly relevant.

ETHICAL DECLARATIONS

Ethics committee approval: This study was approved by the Clinical Researches Ethical Committee of Taksim Training and Research Hospital (Date: 26/06/2019, Decision No: 81).

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. Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology 2009; 49: 306-17.
2. Chatrath H, Vuppalanchi R, Chalasani N. Dyslipidemia in patients with nonalcoholic fatty liver disease. Semin Liver Dis 2012; 32: 22-9.
3. Wree A, Broderick L, Canbay A, Hoffman HM, Feldstein AE. From NAFLD to NASH to cirrhosis-new insights into disease mechanisms. Nat Rev Gastroenterol Hepatol 2013; 10: 627–36.
4. Mehta K, Van Thiel DH, Shah N, Mobarhan S. Nonalcoholic fatty liver disease: pathogenesis and the role of antioxidnats. Nutrition Reviews 2002; 60: 289-93.
5. Emanuele E. Is biopsy always necessary? Toward a clinico-laboratory approach for diagnosing nonalcoholic steatohepatitis in obesity. Hepatology 2008; 48: 2086-7.
6. Calès P, Boursier J, Chaigneau J, et al. Diagnosis of different liver fibrosis characteristics by blood tests in non-alcoholic fatty liver disease. Liver International 2010; 30: 1346-54.
7. Dasarathy S, Dasarathy J, Khiyami A, Joseph R, Lopez R, McCullough AJ. Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study. J Hepatol 2009; 51: 1061–7.
8. Ting YW, Wong SW, Anuar Zaini A, Mohamed R, Jalaludin MY. Metabolic syndrome is associated with advanced liver fibrosis among pediatric patients with non-alcoholic fatty liver disease. Front Pediatr 2019; 7: 491.
9. Mui P, Hill SE, Thorpe RJ Jr. Overweight and obesity differences across ethnically diverse subgroups of Asian American men. Am J Mens Health 2018; 12: 1958-65.
10. Ma H, Xu C, Xu L, et al. Independent association of HbA1c and nonalcoholic fatty liver disease in an elderly Chinese population. BMC Gastroenterol 2013; 13: 3.
11. Ballestri S, Zona S, Targher G, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. J Gastroenterol Hepatol 2016; 31: 936–44.
12. Mustapic S, Ziga S, Matic V, et al. Ultrasound grade of liver steatosis is independently associated with the risk of metabolic syndrome. Can J Gastroenterol Hepatol 2018; 2018: 8490242.
13. Madan K, Batra Y, Gupta SD, et al. Non-alcoholic fatty liver disease may not be a severe disease at presentation among Asian Indians. World J Gastroenterol 2006; 12: 3400-5.
14. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005; 129: 113-21.
15. Collates R, Ong JP, Younossi ZM. Nonalcoholic fatty liver disease and the epidemic of obesitiy. Cleve J Med 2004; 71: 657-64.
16. Weiß J, Rau M, Geier A. Non-alcoholic fatty liver disease: epidemiology, clinical course, investigation, and treatment. Dtsch Arztebl Int 2014; 111: 447-52.
17. Ong JP, Younossi ZM. Epidemiology and natural history of NAFLD and NASH. Clin Liver Dis 2007; 11: 1-16.
18. Vajro P, Lenta S, Socha P, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. J Pediatr Gastroenterol Nutr 2012; 54: 700-13.
19. Makkonen J, Pietiläinen KH, Rissanen A, Kaprio J, Yki-Järvinen H. Genetic factors contribute to variation in serum alanine aminotransferase activity independent of obesity and alcohol: a study in monozygotic and dizygotic twins. J Hepatol 2009; 50: 1035-104.
20. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes 2001; 50: 1844–50.
21. Kissebah AH, Krakower GR. Regional adiposity and morbidity. Physiol Rev 1994; 74: 761–811.
22. Kang SH, Cho Y, Jeong SW, Kim SU, Lee JW. Korean NAFLD Study Group. From nonalcoholic fatty liver disease to metabolic-associated fatty liver disease: Big wave or ripple? Clin Mol Hepatol 2021; 27: 257-69.
23. Pacifico L, Bonci E, Andreoli G, et al. Association of serum triglyceride-to-HDL cholesterol ratio with carotid artery intima-media thickness, insulin resistance and nonalcoholic fatty liver disease in children and adolescents. Nutr Metab Cardiovasc Dis 2014; 24: 737-43.
24. Wong VW, Chu WC, Wong GL, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012; 61: 409-15.
25. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018; 67: 328-57.
26. Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia 2012; 55: 885-904.
27. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015; 63: 237-64.
28. Mofrad P, Contos MJ, Haque M, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003; 37: 1286-92.

Original Article

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Candidate drug molecule-DNA interaction and molecular modelling of candidate drug molecule

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ABSTRACT

Aim: 1,4-dihydropyridine derivative, 1-(3-phenyl propyl)-4-(2-(2-hydroxybenzylidene) hydrazone)-1,4-dihydropyridine (abbreviated as DHP) was synthesized as potential agent for Alzheimer's disease which is a progressive neurodegenerative brain disorder affecting millions of elderly people. With this study, the electrochemical properties of DHP were investigated and its interaction with DNA was analyzed by differential pulse voltammetry (DPV) and cyclic voltammetry (CV) measurements. In addition, this study aims to determine degradation mechanism of the DHP molecule by Density-functional theory (DFT) in gas and in aqueous phase.

Material and Method: Experimental conditions such as immobilization time, the effect of the scan rate, concentration, and the effect of pH were optimized. The method was validated according to validation parameters such as range, precision, linearity, limit of detection (LOD), limit of quantitation (LOQ) and inter/intraday.

Results: Linearity study for the calibration curve of DNA and DHP with DPV was calculated in the calibration range 10-100 µg/mL. The LOD and LOQ values were calculated as 3 and 10 µg/mL and intra-day and inter-day repeatability (RSD %) were 1.85 and 3.64 µg/mL, respectively. After the DHP-DNA interaction, the oxidation currents of guanine decreased as a proof of interaction. The activation energy of the most possible path of reaction was calculated, and their thermodynamically most stable state was determined in gas phase.

Conclusion: We developed to improve a sensitive, fast and easy detection process for determination of interaction between DHP and DNA.

Keywords: DNA, candidate drug molecule, DNA-drug interaction, biosensor, DFT

INTRODUCTION

Electrochemical biosensors have an important impact on environmental monitoring, clinical diagnosis and pharmaceutical studies. From the electrochemical studies, useful information can be attained with regard to redox process (1). DNA biosensors offer fast, basic, and high sensitivity and they are inexpensive in the determination of drug-DNA interaction. They consist of a nucleic acid recognition layer immobilized to the electrochemical transducer. The nucleic acid recognition layer detects changes in DNA structure or the specific sequence of DNA that occurs during the interaction of DNA and binding molecules (2-5). The interaction of drugs with DNA is one of the main targets in drug discovery. The search for a drug-DNA interaction has a significant effect on understanding the mechanism of interaction in order to design more efficient drugs. Drug and DNA interaction studies associated with ligands that bind DNA such as intercalation, cross linking, non-covalent binding and covalent binding do exist in literature. The different molecular interaction types such as electrostatic, van der Waals, hydrogen bonding, dipole-dipole and π-π interactions cause different pharmacological effects (6-8). The specificity, speed, portability and low-cost usage of biosensors enable them to be utilized in many areas from clinical applications to pharmaceutical research, from food analysis to agricultural analysis. It can be observed that the analysis results are more specific and sensitive for the detection of hereditary diseases and contagious infections (9). The results of the analysis of substance-DNA interaction are obtained by monitoring the changes

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in the signals of the substance itself or the electrophilic bases in the DNA structure. Wang et al. (10) investigated daunomycin and DNA interaction in solution phase by using carbon paste electrode, and Dogan-Topal et al. (11) analyzed Leuprolide and DNA interaction and guanine signals decreased after the interaction with leuprolide in their study.

In this study, DNA interactions of the synthesized compound DHP were analyzed with the help of electrochemical methods. DHP was previously synthesized as a potential compound for Alzheimer's disease (AD) (12). Alzheimer's disease is one of the leading causes of death among elderly people in the world (13). Existing drugs have been unable to combat or reverse the progression of the disease. This is due to the complex and multifactorial nature of AD. A great deal of research has been devoted to the development of new anti-AD agents. There are many studies based on the treatment of AD with different heterocyclic scaffolds (14). Efforts have also been made towards the development of pyridine scaffolds as anti-AD agents (15). One of the most popular methods for the preparation of pyridines is the oxidation of corresponding 1,4-dihydropyridines. 1,4-dihydropyridine is viewed as a privileged scaffold as a brain-targeting chemical delivery system (CDS) which is based on the dihydropyridine-pyridinium type redox conversion of a lipophilic dihydropyridin (16). Due to the therapeutic role of the pyridine (17-20) derivatives and the pharmaceutical effects of 1,4-dihydropyridine compounds (12,21,22), in this study we intend to explore the effects of a 1,4-dihydropyridine derivative. **Figure 1** shows molecular structure of DHP. We aim to develop novel electrochemical DNA biosensor for DHP and DNA interaction. The goal of the study is to determine a predicted degradation pathway for DHP molecular structure in gas and aqueous phase. Most possible reaction pathway for DHP molecular structure to occur with OH radicals was determined by employing density functional theory (DFT) method.

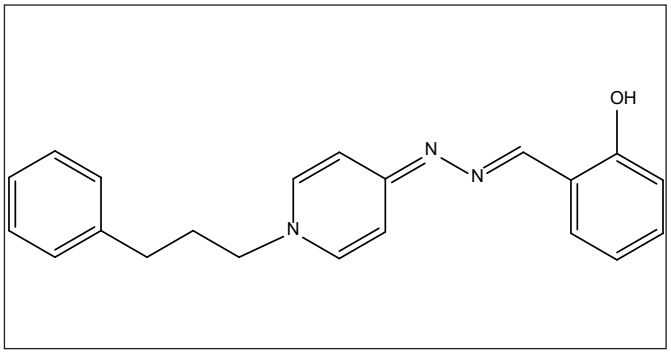

Figure 1. Molecular structure of DHP.

MATERIAL AND METHOD

The ethics committee approval isn't required in the article.

Chemistry

Apparatus and instruments: The IR spectra of the compound was monitored by attenuated total reflectance (ATR) (PerkinElmer Spectrum 100 FT-IR, Shelton, USA). ^{1}H NMR spectra was recorded with a Varian AS 400 Mercury Plus NMR spectrometer (Varian, Palo Alto, CA, U.S.A.) operated at 400 MHz. in deutero-DMSO. Abbreviations for data quoted are: s (singlet), t (triplet), quin (quintet), m (multiplet), dd (doublet-doublet). Mass spectra (ESI-MS) was measured on a Thermo MSQ Plus LC/MS (Thermoscientific Inc., San Jose, CA). All chemicals used for synthesis were purchased from Sigma, Acros, Fluka, and Merck companies.

Synthesis of the compound DHP: The synthesis of the final compound DHP was prepared in three steps in our previous study (12). In the first step, a solution of 4-chloropyridine (0.1 mol) and hydrazine monohydrate (0.2 mol) in 1-propanol (30 mL) was refluxed for 18h. The solution was cooled to 0°C and the precipitate was filtered, washed with cool 1-propanol and crystallized from ethanol. In the second step, 4-hydrazinylpyridine (7.5 mmol) was condensated with 2-hydroxybenzaldehyde in ethanol (30 mL) to obtain hydrazone intermediate. The precipitate was filtered and washed with cool ethanol/water (1:1) mixture and crystallized from ethanol. In the third step, a mixture of hydrazone intermediate (0.01 mol) and 3-phenylpropyl bromide (0.02 mol) were refluxed in ethanol. The mixture was cooled to room temperature. The precipitate was filtered and washed with cool ethanol. The crude product was crystallized from ethanol. Then, it was converted to its' 1,4-dihydropyridine form after being treated with sodium hydroxide solution.

Spectral data of compound DHP: IR (KBr) cm^{-1}: 3025, 2925, 2856, 1646, 1598, 1513, 1454, 1400, 754, 700. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.39 (1H, s, N=CH), 7.47 (1H, dd, J= 2.0, 7.8 Hz, Ar-H), 7.39-7.33 (2H, m, Pyr-H), 7.29-7.15 (6H, m, Ar-H), 6.87-6.84 (2H, m, Ar-H), 6.50 (1H, dd, J= 2.7, 7.4 Hz, Pyr-H), 6.21 (1H, dd, J= 2.7, 7.4 Hz, Pyr-H), 3.78 (2H, t, J= 7.2 Hz, N-$\underline{CH_2}$-CH_2-CH_2-Ph), 2.55 (2H, t, J= 8.0 Hz, N-CH_2-CH_2-$\underline{CH_2}$-Ph), 1.97 (2H, quin, J= 7.4 Hz, -N-CH_2-$\underline{CH_2}$-CH_2-Ph). ESI-MS m/z: 332 (M+H).

DNA and Candidate Drug Molecule

Reagents and chemicals: Double stranded deoxyribonucleic acid (dsDNA) obtained from fish sperm and KH_2PO_4, K_2HPO_4, $K_3(Fe(CN)_6$, $K_4(Fe(CN)_6$, CH_3COOH, NaCl, NaOH were supplied from Sigma-Aldrich.

Apparatus and instruments: AUTOLAB-PGSTAT 30 electrochemical analysis system was studied in voltammetric measurements. A pencil graphite electrode (PGE) (Tombow 0.5 HB) was used as the working electrode, a Ag/AgCl electrode was employed as the reference electrode, and a platinum wire was used as the counter electrode. μ- AUTOLAB with NOVA software was used in DPV and CV measurements.

Preparation of Solutions

Preparation of DHP: Alptuzun et al. (12) synthesized the final molecule. The chemical name of the molecule is 1-(3-phenyl propyl)-4-(2-(2-hydroxybenzylidene) hydrazone)-1,4-dihydropyridine (abbreviated as DHP). Figure 1 shows the chemical structure of DHP. 1 mg DHP was dissolved in DMSO (dimethyl sulfoxide). Stock solutions of DHP were diluted with BBS. Each pretreated electrode was immersed into the vials containing DHP solution (40 μg/mL) during 5-90 min. Immobilized electrodes were rinsed with BBS.

Preparation of DNA: Double stranded DNA (ds-DNA) (abbreviated as DNA) from fish sperm was used. 1 mg DNA was prepared in purified water. Stock solutions of DNA was diluted with PBS. Activated electrodes were immersed in 200 μg/mL of DNA solution for 5-60 min. and DNA immobilized electrodes were rinsed with PBS.

Preparation of buffer solutions: 0.5 M acetate (pH 4.8), 0.05 M phosphate (pH 7.4) and 0.10 M borate buffer solutions (pH 8.1) were prepared by diluting with 20 mM NaCl.

Method

Electrode Activation: The PGEs surface were activated by application of +1.40 V for 30 s in ACB in order to oxidize -COOH groups of the PGEs. Passive adsorption was used for the immobilization of DHP and DNA.

Interaction of DNA with DHP: Firstly, PGEs were immobilized with DNA. DNA coated electrodes were immersed into the vials containing 40 μg/mL DHP solution prepared in BBS for during 5-45 min. DHP and DNA immobilized electrodes were rinsed with PBS and BBS, respectively.

Measurement

ACB was used in all DPV measurements. The oxidation signals were measured by scanning from +0.3 V to +1.2 V potential range vs. Ag/AgCl/3 M reference electrode. 20-100 mV/s were used for the scan rate measurements. 10 mM $K_3(Fe(CN)_6/K_4(Fe(CN)_6$ solution was used for CV measurements.

Methodology and Computational Set-up

Computational models: The molecules were modelled by using distances of mean bonds and the geometrical parameters corresponding to the benzene ring. For the computational modeling; (i) the sp^3-hybridized carbon that formed tetrahedral angles was employed and (ii) the sp^2-hybridized C-O atoms that composed 120° angles were employed. The planar aromatic ring kept unchanged, excluding the position of attack. It was presumed that the C–H bond was creating a tetrahedral angle with the attacking •OH. This phenomenon is explained in the literature as the hybridization state change of the carbon atoms from sp^2 to sp^3 at the addition center (23).

In photocatalytic degradation reactions of DHP, some products that are more harmful than that original material contains could be formed. The reactions of photocatalytic degradation for DHP along with its hydroxy derivatives were directly correlated with the reaction of •OH with these molecules, since the production yield was the same. Therefore, the analysis of theoretical reaction kinetics of DHP was conducted only for •OH. The study started with the initiation of DHP and then continued with the exposure of •OH in order to complete the reaction. The reaction yields were modelled and calculated in gas phase. Experimental results found in literature showed that the detachment of a hydrogen atom from saturated hydrocarbons by •OH was realized first, and then unsaturated hydrocarbons along with the materials with similar structure received the previously mentioned •OH (24). For this purpose, the determination of possible reaction pathways was studied thoroughly for the analyzed reactions. Density functional theory (DFT) was utilized for the electronical orbital calculations of the reactant molecule, yield, and transition state complexes, which were realized for each reaction path, along with their optimized geometries. In order to conduct the conformational analysis of the structures, a potential energy surface (PES) scan using the B3LYP/6-31G* method was performed in a relaxed manner, which meant optimization criteria was reached for each point, along with the torsional coordinates for both conformers (25).

Methodology: Optimized geometry of the reactants, the products, and the transition state complexes were calculated with DFT method via the Gaussian 09 software (26). DFT methods utilize the precise electron density in order to compute properties of the molecular structure and electronic energy levels, which includes electron correlation, as well. For open-shell systems, spin contamination is not an issue of concern, therefore this type of calculation becomes favourable. The combination of the Hartree-Fock and Becke exchange terms along with the Lee–Yang–Parr correlation functional which created the hybrid B3LYP functional were a good fit for the DFT calculations that were conducted in this study (23).

The determination of the basis set for the calculations is of utmost importance. The study employed a popular and well-studied B3LYP/6-31G(d) level. For the transition state determination, the reaction coordinates were defined as the forming C–O bonds in the addition paths. As in abstraction paths, the forming of H–O bond was defined. The structures for ground state and transition state were approved by conducting a frequency analysis study at the previously mentioned level. The characterization of the transition structures was established by detecting one imaginary frequency. This frequency corresponded to a first-order saddle point, belonging to the reaction coordinate. The B3LYP/6-31G(d) level was also used for the calculations of zero-point vibrational energies (ZPEs) (23).

RESULTS

Optimization Conditions of DNA

Optimum conditions for DNA immobilization are given in **Figure 2**. DNA was prepared in pH 4.8 ACB, pH 7.4 PBS (20 mM NaCl) and 7.4 PBS (500 mM NaCl) buffer solutions. The effect of buffer solution is presented in **Figure 2A**. The highest oxidation currents of guanine were found in PBS (20 mM NaCl), so DNA solutions were prepared in PBS (20 mM NaCl). To determine the optimum concentration of DNA, DNA solutions were prepared in PBS so that they could be in the range of 5–100 µg/mL (**Figure 2B**). Oxidation currents of guanine ascended together with increasing DNA concentration and then leveled off. 100 µg/mL of DNA was used for optimum DNA concentration because the highest peak current was observed. For optimization of the immobilization time, DNA was immobilized during 5- 60 min (**Figure 2C**)

The oxidation currents of guanine increased for 30 min and then started to decrease so 30 min was chosen for an optimum immobilization time**.**

Optimization Conditions of DHP

Optimization conditions of DHP were investigated. DHP has an irreversible anodic peak potential at +0.8 V. Figure 3A and 3B show experimental results such as immobilization time and concentration. pH 4.8 (ACB), pH 7.4 (PBS) and pH 8.1 (BBS) buffer solutions were analyzed for optimum pH. The highest DHP oxidation signals were obtained in BBS. In order to find the optimum concentration of DHP, DHP solutions were prepared in BBS so that the final concentrations could be in the range of 10–100 µg/mL. (**Figure 3A)**. The maximum signal was detected at 100 µg/mL but 40 µg/mL DHP was used in the experiments because reproducible and sufficient signal was obtained in 40 µg/mL. The effect of immobilization time is given in **Figure 3B**.

To determine optimum immobilization time of DHP, DHP was immobilized during 10-90 min. The oxidation signals of DHP increased with the time and remained stable after 45 min. 45 min was used for optimum immobilization time. The calibration curves (y=mx+n) were constructed by the plots of the peak current (y) of DHP versus the concentrations (x) of the calibration standards. Linearity was observed in the range 10-100 µg/mL.

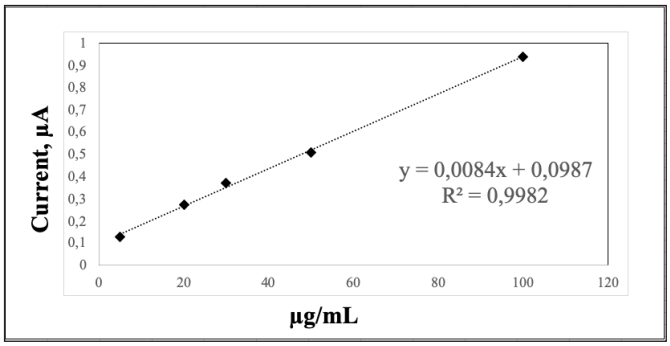

Figure 2B. Average current of guanine oxidation signals measured with DNA for different concentration. (n:5)

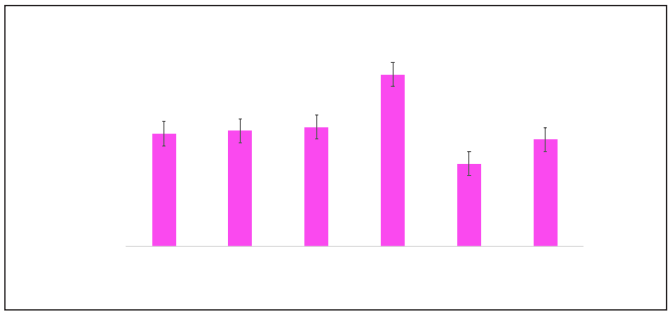

Figure 2C. Average current of guanine oxidation signals measured with DNA for different immobilization time (n:5).

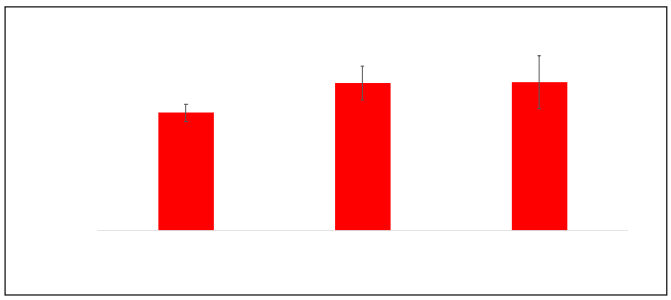

Figure 2A. Average current of guanine oxidation signals measured with DNA for different pH (n:5)

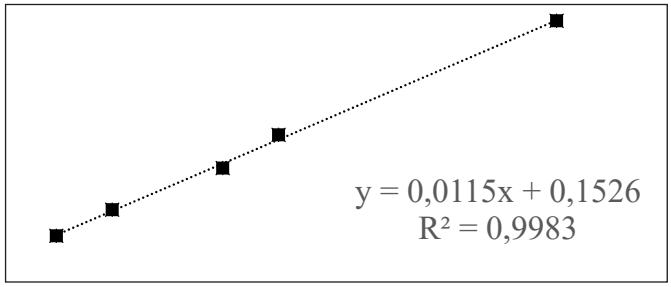

Figure 3A. DHP current corresponding to the oxidation signal for different concentration. (n:5)

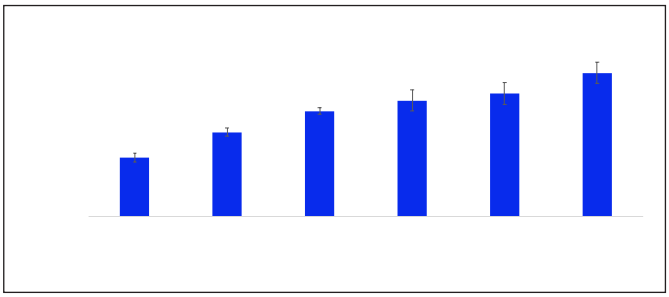

Figure 3B. DHP current corresponding to the oxidation signal for different immobilization time. (n:5)

The regression equation: y=0.0115x+0.1526 (R^2:0.9983)

where y is the peak current, and x is the concentration of DHP in µg/mL. LOD and LOQ were calculated to be 3.3 σ/m and 10 σ/m, respectively, where m is the slope of the calibration curve and σ is the standard deviation of the intercept of the regression equation (27). Values of LOD and LOQ were calculated to be 3 and 10 µg/mL, respectively. Different three concentrations were measured in three replicates during the same day and three consecutive days to determine the precision and accuracy of developed method. The precision of the method was given as the relative standard deviation (RSD %). The intra- and inter-day precision values were found to be 1.85 and 3.64 µg/mL.

Effect of Scan Rate

Scan rate studies were carried out with CV. It was investigated whether it was diffusion or adsorption controlled in order to determine the effect of the scan rate. The results for the effect of the scan rate are given in **Figure 4**.

As it is seen from Figure 4, the peak currents of DHP increased with increasing scan rate (10 to 100 mV/s).

The equations peak current versus scan rate for 40 µg/mL DHP prepared in BBS are as follow:

Ip1 (µA)=0.0668(mVs^{-1})+0.3912 (R^2=0.9967) for the first peak

Ip2 (µA)=-0.007(mVs^{-1}) - 0.25 (R^2=1.00) for the second peak

The slope of the above equations are close to the theoretical value of 0.5, which proved the occurrence of a diffusion-controlled electrode process for the first and second peak according to these results (30).

The electrochemical reaction was found as diffusion controlled. The equations peak current versus the root of scan rate are as follow:

Ip1 (µA)=0.8883$v^{1/2}$(mVs^{-1})$^{1/2}$ -2.0878 (R^2=0.9864)

Ip2 (µA)=-0,1016$v^{1/2}$(mVs^{-1})$^{1/2}$+0.0832 (R^2=0.9882)

Effect of pH

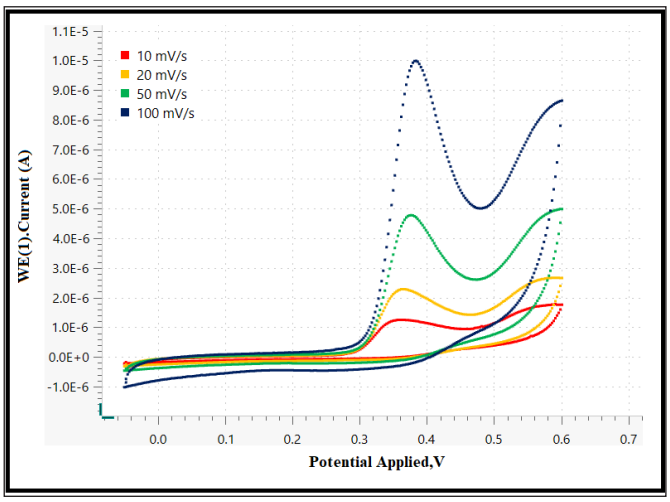

Figure 4. Cyclic voltammograms of DHP at different scan rates (10–100 mV/s). (n:5)

The effect of pH was investigated with CV. DHP oxidation signal values obtained at different pH 's are given in **Figure 5**. DHP was prepared and measured in ACB (4.8), PBS (7.4) and BBS (8.1). The order of the pH was determined to be PBS> BBS> ACB. The peak potential values were observed from+0.35 V to+0.6 V.

Interaction

DNA and DHP interaction was investigated to explain the effect of DHP on DNA. DHP and DNA were interacted in different interaction times (5-45 min) by DPV (**Figure 6**). After the interaction with DHP, guanine oxidation signals decreased. 15 min was selected as the optimum interaction time.

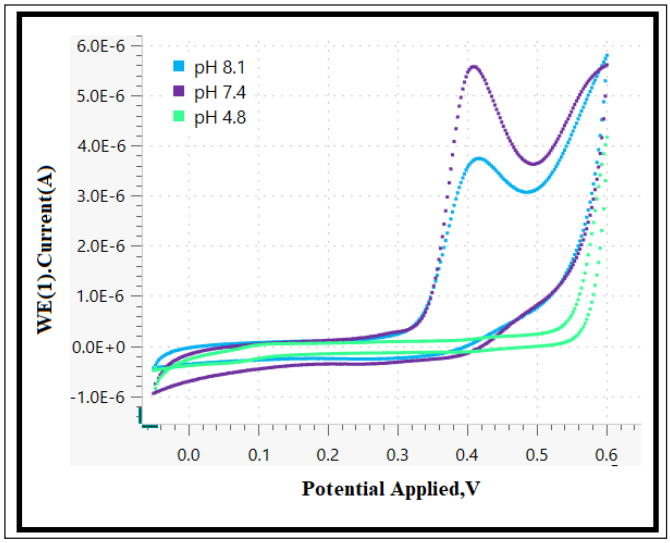

Figure 5. Cyclic voltammograms of DHP at different pH.

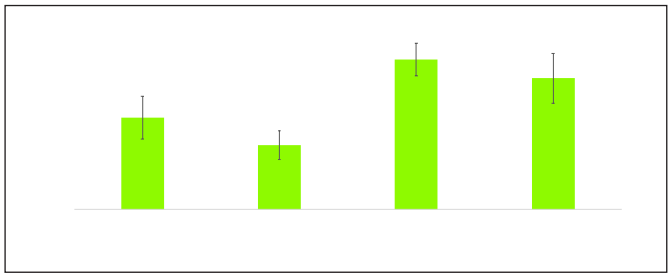

Figure 6. Histogram of oxidation currents of DNA and DHP interaction. (n:5)

Molecular Modeling

DFT reactivity descriptors were used in order to have a deeper understanding of the most susceptible radical attack sites for hydroxyl, which in turn enlightens the photocatalytic degradation reaction of DHP. The molecular geometry of DHP molecule and the numbering system, which is optimized with previously mentioned method and level that is used along the calculations (**Figure 7**).

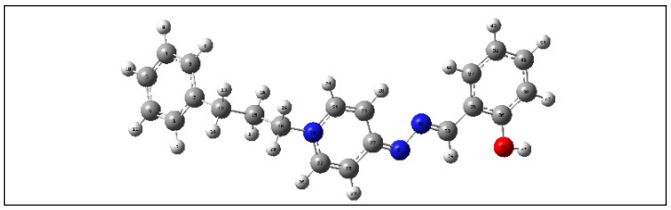

Figure 7. Optimized structure of DHP and the numbering system (gray, carbon; red, oxygen; blue, nitrogen; white, hydrogen).

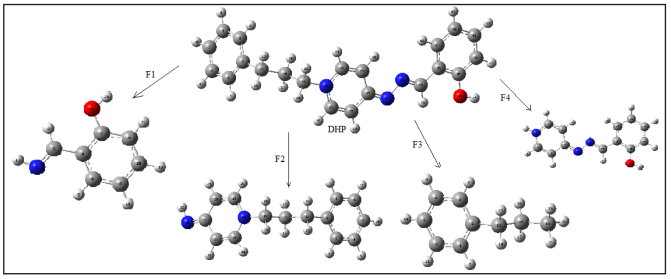

Figure 8. Possible pathways for the photocatalytic degradation of DHP.

Three most probable reaction paths are shown in **Figure 8**. The close softness values to the •OH radical of these paths were the selection criteria. It is well-known that the most stable structure geometry corresponds to the lowest-energy structure of the molecule. Constant energy, Enthalpy and Gibbs free energy values visualized by DFT are given **Table 1.**

Table 1. Constant energy, Enthalpy and Gibbs free energy values according to DFT Method

Molecules	Energy (kcal/mol)	Enthalpy (kcal/mol)	Gibbs free energy (kcal/mol)
DHP	-660082.807	-660082.215	-660131.909
F1	-251490.149	-251489.557	-251515.028
F2	-409335.277	-409372.334	-409372.134
F3	-219627.906	-219627.314	-219654.847
F4	-441197.817	-441197.225	-441232.324

DISCUSSION

Voltammetric signals of dsDNA electroactive bases were used for interactions between drug and DNA and DNA and drug interactions, which explain changes in the electrochemical responses of DNA before and after the interaction with drugs. As a simple method of base immobilization for working electrodes, physical adsorption is widely utilized. This method also eliminates the requirement for modifications and chemical reagents. In our study, physical (passive) adsorption was used for DNA immobilization on pencil graphite electrodes (28-30) As a rule of thumb, the researches of electrochemical based DNA-drug interaction, which are mostly label free, depend on the alterations in variations in the oxidation indicators of guanine bases due to the fact that guanines are the most electroactive bases within thymine, cytosine and adenine. Guanines have high levels of oxidation capacity at +1.0 V (versus reference electrode) whereas sugar and phosphate backbone, which generate other parts of nucleic acids, are non-electroactive. Utilizing guanine bases as in electrochemical studies provides an opportunity as pencil graphite, carbon and gold electrodes adsorb them without any difficulty (28). If DHP and DNA are not immobilized on the surface of PGEs , the guanine signals cannot be obtained and repeated.

100µg/mL of DNA concentration was utilized since it led to the most steady signals with the highest intensity. Immobilization time is shown to be one of the most important experimental parameters in effective DNA immobilization onto the surface of the electrode The immobilization time differed from 5 minutes, up to 60 minutes for DNA. The DNA oxidation currents correlated with time, but started to decrease after 30 minutes, which meant that the selected DNA immobilization time was 30 min. Irreversible anodic peak potential of DHP is determined to be +0.8V. The potency of oxidation for phenolic groups are known to exist, as well as the electrochemical oxidation capacity in hydrazone group of DHP. The electrochemical reactions, hydrazone and phenol groups in particular are highly active for the electrochemical behaviors of DHP. Concentration, pH and immobilization time of DHP were kept optimal as parameters. The investigation of the effect of buffer solution was realized over a broad range of pH values, from acidic to basic. BBS led to the highest oxidation signal of DHP oxidation. 40 µg/mL of concentration was used throughout the study, showing a better producible and more satisfactory signal. Immobilization time was changed from 10 minutes to 90 minutes for DHP The increasing of signal was observed by time, which remained almost constant after 45 minutes. 45 min was picked as DHP immobilization time.

Developed method was validated according to parameters of LOD, LOQ, linearity, accuracy and precision. Linearity was observed between 10 to 100 µg/mL concentration**.** The LOD and LOQ values were calculated to be 3 and 10 µg/mL, respectively.

Calibration curves (y=mx+n) were constructed using plots of the peak currents (y) of DHP versus the concentrations (x) of the calibration standards.

Accuracy of method were investigated with intra- and inter-day analyses. For each analyte, three different concentrations were analyzed for intra- and inter-day analyses. Precision of method was obtained from the relative standard deviation (RSD%). The intra- and inter-day precision values were 1.85 and 3.64 µg/mL, respectively. To be more specific, when studying reaction mechanisms on the electrode surface and kinetics parameters as well as oxidation and reduction properties, important and valuable information can be obtained. Thanks to our experiments, scan rates and peak current/ potential relationships as well as the kinetic data have been determined. CV is utilized for the determination of the electrochemical data, scan rates and the effect of pH for 40 µg/mL DHP. The shape of the voltammogram is heavily affected by pH of the supporting electrolyte, providing valuable data with regard to the process of electrode that electrons and protons participate in. Hence, the investigation of the effect of pH on the candidate drug is of utmost importance. The highest peak current was acquired by PBS, which is chosen for pH measurements.

CV is also utilized for scan rate study, which helps to determine the diffusion or adsorption controlled process. Physical adsorption of DHP onto the untreated electrode surface was determined by the increased current with scan rate.The potentials of the peaks are also shifted to larger voltage values from +0.3V to +0.6V. 100mV/s scan rate was chosen in order to determine the DHP, for sharp and well-defined signals. Presence of DNA might change the current and peak potential of drug molecule in case of interaction with the compound. Irreversible nature of electron transfer process is verified by positive shift in peak potentials.

To investigate the interaction between guanine and DHP signal, DHP-DNA effect experiments have been conducted. In DPV measurements, 40 µg/mL DHP immobilized PGEs were dipped into 100 µg/mL DNA solution. DHP and DNA were interacted for 5-45 min. The interaction time was chosen as 15 min because the highest oxidation signal differences were obtained between after and before interaction durations.

DHP and guanine oxidation signals were measured in after and before interaction. A decrease has been noted in guanine current signals following DNA-DHP interaction. This decrease is due to the binding of DHP on DNA, which leads to a compact DNA structure. Hence, oxidation after the interaction becomes more difficult, therefore the guanine oxidation peak currents decrease.

The decrease might be rationalized as a probable harm or defense/security of the oxidizable groups of guanine base in the interim of a candidate molecule interaction with DNA on PGE surface. To detect DNA sites and rational formation/construction of new DNA-targeted molecules, a-such experiments play a vital role. Histogram of oxidation currents of DNA and DHP interaction are presented in **Figure 6**. In addition, the oxidation signals of DHP decreased after its interaction with DNA. In literature, there are many studies which guanine oxidation signal decreases after drug and DNA interaction. However, the decrease or increase redox signals of drug molecules are infrequent (31,32).

The interaction with DHP decreased the current signals of guanine dramatically. The decrease in the DNA oxidation peak currents could be explained as a consequence of the binding of DHP to DNA. The possible reason could be DHP and DNA interaction causes more complex DNA structure and therefore causing oxidization to be more difficult and resulting in a decrease of peak currents for guanine oxidation. The oxidation signal of DHP decreased significantly after the interaction with DNA that confirmed DHP-DNA interaction, leading to DNA structural changes.

In literature, there are studies relevant to DNA-drug interactions of pyridine derivatives analyzed by electrochemical methods. Topkaya et al. (30) investigated DNA and drug interaction of 4-Pyri molecule. They observed that after the interaction with drug molecule, the intrinsic oxidation currents of drug molecule increased while DNA's oxidation currents decreased. In another study, the interaction between pyridine derivate molecule and DNA was analyzed electrochemically. According to the results, it was observed that the oxidation signal of the pyridine derivative increased after its interaction with DNA, while the oxidation signal of guanine decreased (31). In our study, however, oxidation signals of both DNA and candidate drug molecule decreased after DNA and drug interaction. Marin et al. (33) and Teijeiro et al. (34) analyzed the interactions of Mitomycin C and Anthramycin with DNA. They obtained that oxidation signals of DNA and drug molecules decreased after interaction. We obtained similar results in our study showing that DNA and drug molecule's oxidation signals decrease. Wang et al. (35) investigated Promethazine and DNA interactions and they showed that the oxidation signal of Promethazine after its interaction with DNA increased, while the oxidation currents of guanine decreased.

The path for most possible reaction of DHP molecule to occur with OH radicals was analyzed. Gaussian 09 software was utilized for the calculation of optimized geometry and the calculation results were visualized via GaussView 5 software. Subsequently, the determination of the lowest energy states was also conducted by optimization of geometric parameters via Gaussian 09 software. DFT method is employed for the determination of the intermediates for mechanism of photocatalytic degradation relating to DHP, along with the optimization of the structure. Activation energy of the most possible path of reaction was calculated, and their thermodynamically most stable state was determined in gas phase.

CONCLUSION

The electrochemical properties of DHP and interaction between DNA+ DHP were studied for the first time. The interaction between DNA and DHP was measured by DPV. We observed changes in the oxidation signal of DHP and guanine bases of DNA after interaction. The investigations of drug-DNA interaction may provide new compounds to be analyzed for a possible effect on a biomolecular target. In addition, our study enabled a sensitive, fast and easy detection process for interaction between DHP and DNA. The prediction of DHP degradation occurred through intramolecular F1, F2, F3 and F4 ring cleavages, which in turn followed by subsequent •OH radical reactions. The fragments transform into smaller species by this reaction, such as CO_2, NO_3^- and NH_4^+.

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REFERENCES

1. Diculescu VC, Oliveria-Brett AM. In situ electrochemical evaluation of DNA in- teraction with the anticancer drug danusertib nitrenium radical product using the DNA-electrochemical biosensor. Bioelectrochemistry 2016; 107: 50–7.
2. Wang J. Electrochemical biosensors: Towards point-of-care cancer diagnostics. Biosensors and Bioelectronics 2006; 21 :1887-92.
3. Palecek E. Oscillographic polarography of highly polymerized deoxyribonucleic acid. Nature 1960; 188: 656-7.
4. Erdem A, Ozsoz M. Electrochemical DNA biosensors based on DNA-drug interactions. Electroanalysis 2002; 14: 965-74.
5. Rauf S, Gooding JJ, Akhtar K, et al. Electrochemical approach of anticancer drugs-DNA interaction. J Pharm Biomed Anal 2005; 37: 205-17.
6. Egli M, Flavell A, Pyle AM, et al. Nucleic acids in chemistry and biology. 3th ed. Cambridge- UK: The Royal Society of Chemistry; 2006.
7. Yang M, McGovern ME, Thompson M. Genosensor technology and the detection of interfacial nucleic acid chemistry. Anal Chim Acta 1997; 346: 259-75.
8. Morales KD, Alarcon-Angeles G, Merkoci A. Nanomaterial-based sensors for the study of DNA interaction with drugs. Electroanalysis 2019; 31: 1845-67.
9. Zheng Y, Yang C, Pu W, Zhang J. Carbon nanotube-based DNA biosensor for monitoring phenolic pollutants. Microchim Acta 2009; 166: 21–6.
10. Wang J, Ozsoz M, Cai XH, et al. Interactions of antitumor drug daunomycin with DNA in solution and at the surface, Bioelectrochem Bioenerg 1998; 45: 33–40.
11. Dogan-Topal B, Ozkan SA. A novel sensitive electrochemical DNA biosensor for assaying of anticancer drug leuprolide and its adsorptive stripping voltammetric determination. Talanta 2011; 83: 780-8.
12. Prinz M, Parlar S, Bayraktar G, et al. 1,4-Substituted 4-(1H)-pyridylene-hydrazone-type inhibitors of AChE, BuChE, and amyloid-β aggregation crossing the blood-brain barrier. Euro J Pharm Sci 2013; 49, 603-13.
13. Sameem B, Saeedi M, Mahdavi M, Shafiee A. A review on tacrine-based scaffolds as multi-target drugs (MTDLs) for Alzheimer's disease. Euro J Med Chem 2017; 128: 332-45
14. Jalili-Baleh L, Nadri H, Moradi A, et al. New racemic annulated pyrazolo[1,2-b]phthalazines as tacrine-like AChE inhibitors with potential use in Alzheimer's disease. Eur J Med Chem 2017; 139: 280-9.
15. Reddy MVK, Rao KY, Anusha G, et al. In-vitro evaluation of antioxidant and anticholinesterase activities of novel pyridine, quinoxaline and s-triazine derivatives. Environ Res 2021; 199: 111320.
16. Bodor N, Buchwald P, Barriers to remember: brain-targeting chemical delivery systems and Alzheimer's disease. Drug Discov Today 2002; 7: 766-74.
17. Alptuzun V, Parlar S, Tasli H, Erciyas E. Synthesis and antimicrobial activity of some pyridinium salts.molecules. 2009; 14: 5203-15.
18. Chang Y, Jin L, Duan JJ, Zhang Q, Wang J, Lu Y. New conjugated poly(pyridinium salt) derivative: AIE characteristics, the interaction with DNA and selective fluorescence enhancement induced by DNA. RSC Advances 2015; 125: 103358-64.
19. Xie BP, Qiu GH, Hu PP, et al. Simultaneous detection of Dengue and Zika virus RNA sequences with a three-dimensional Cu-based zwitterionic metal-organic framework, comparison of single and synchronous fluorescence analysis. Sensors and Actuators B: Chemical 2018; 254: 1133-40.
20. Sun JF, Lu Y, Wang L, et al. Fluorescence turn-on detection of DNA based on the aggregation-induced emission of conjugated poly(pyridinium salt)s. Polymer Chem 2013; 14: 4045-51.
21. Ţintaş ML, Azzouz R, Peauger L, et al. Access to highly enantioenriched donepezil-like 1,4- dihydropyridines as promising anti-Alzheimer prodrug candidates via enantioselective Tsuji allylation and organocatalytic aza-ene-type domino reactions. J Org Chem 2018; 83: 10231-40.
22. Babu MN, Elumalai K, Srinivasan S, et al. Synthesis and anticholinesterase activity of a novel series of acetazolamide condensed 1,4-dihydropyridines. Carbon Resour Convers. 2019; 2: 191-7.

23. Hatipoglu A, Vione D, Yalcin Y, Minero C, Cinar Z. Photo-oxidative degradation of toluene in aqueous media by hydroxyl radicals. J Photochem Photobiol A: Chem 2010; 215: 59-68.
24. Atkins PW. Physical Chemistry. 6th ed. New York: Oxford University Press; 1998.
25. Mierzejewska KK, Trylska J, Sadlej J. Quantum mechanical studies of lincosamides. J Mol Model 2012; 18: 2727-40.
26. Gaussian 09. Revision B.04. Gaussian, Inc. Pittsburgh-PA; 2009.
27. Little TA. Method validation essentials, limit of blank, limit of detection, and limit of quantitation. Biopharm Int 2015; 28: 48-51.
28. Palecek E. Adsorptive transfer stripping voltammetry: effect of electrode potential on the structure of DNA adsorbed at the mercury surface. Bioelectrochem Bioenerg 1992; 28: 71–83.
29. Kilic T, Topkaya SN, Ozkan Ariksoysal D, et al. Electrochemical based detection of microRNA, mir21 in breast cancer cells. Biosensors and Bioelectron 2012; 1: 195-201.
30. Topkaya SN, Karasakal A, Cetin AE, Parlar S, Alptuzun V. Electrochemical characteristics of a novel pyridinium salt as a candidate drug molecule and its interaction with DNA. Electroanalysis 2020; 32: 1780-87.
31. Karasakal A, Parlar S, Alptuzun V, Cetin AE, Topkaya SN. A novel molecule: 1-(2,6 dichlorobenzyl)-4-(2-(2-4-hydroxybenzylidene) hydrazinyl) pyridinium chloride and its interaction with DNA. Electroanalysis 2021; 33: 1819–25.
32. Aftab S, Kurbanoglu S, Ozcelikay G, et al. Carbon quantum dots co-catalyzed with multiwalled carbon nanotubes and silver nanoparticles modified nanosensor for the electrochemical assay of anti-HIV drug Rilpivirine. Sensor Actuat B-Chem 2019; 285: 571-83.
33. Marin D, Perez P, Teijeiro C, Palecek E. Voltammetric determination of mitomycin C in the presence of other anti-cancer drugs and in urine. Analytica Chimica Acta 1998; 358: 45-50.
34. Teijeiro C, Red E, Marin D. Electrochemical analysis of anthramycin: hydrolysis, DNA-interactions and quantitative determination. Electroanalysis 2000; 12: 963-8.
35. Wang J, Rivas G, Cai X, et al. Accumulation and trace measurements of phenothiazine drugs at DNA-modified electrodes. Anal Chim Acta 1996; 332: 139-44.

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The potential association of musculoskeletal pain with presenteeism and work engagement among intensive care unit nurses: a cross-sectional study

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ABSTRACT

Aim: Work-related musculoskeletal disorders and associated musculoskeletal pain among intensive care nurses are important, as these factors may be related to presenteeism and work engagement. The aim of this study was to investigate the potential association of musculoskeletal pain with presenteeism and work engagement among intensive care nurses.

Material and Method: This descriptive study was carried out with members of the Turkish Society of Critical Care Nurses. All the participants completed a questionnaire, which included questions about general demographic data and occupational musculoskeletal exposures (Occupational Safety and Health Administration [OSHA] Ergonomic Assessment Checklist). To measure pain, work engagement and presenteeism, the following instruments were used: The Brief Pain Inventory Short Form (BPI SF), Utrecht Work Engagement Scale (UWES-17) and Stanford Presenteeism Scale-6 (SPS-6). This study was performed in 2021, and the questionnaire was distributed via email to the database of Turkish Society of Critical Care Nurses.

Results: Our study was completed with 153 intensive care unit nurses. Among the study population, 76.5% (n=117) of the nurses had chronic musculoskeletal pain, 80% of whom had exposure to lifting heavy weights. There was a weak negative correlation between pain and work engagement, as shown by the BPI SF pain interference subscale and the vigour subscale of the UWES-17 (p=0.04, r=-.166). There was also a weak negative correlation between pain and presenteeism according to the BPI SF pain interference subscale and SPS-6 (p=0.04, r=-.193). There was no statistically significant association between workplace ergonomic exposures, presenteeism, work engagement and the presence of chronic musculoskeletal pain.

Conclusion: Neither chronic musculoskeletal system pain nor pain intensity was significantly correlated with work engagement, occupational musculoskeletal exposures or presenteeism. However, musculoskeletal pain-related effects on daily activities of living had a negative impact on work engagement (vigour) and presenteeism.

Keywords: Presenteeism, intensive care nurses, musculoskeletal pain, work engagement, workplace exposure

INTRODUCTION

Work-related musculoskeletal disorders are one of the most important health problems among healthcare workers, with such disorders reported to be a major cause of sickness absence among nurses (1). According to previous studies, approximately 50% of nurses have complained of work-related back pain (2,3). In a Turkish study on healthcare workers, the prevalence of musculoskeletal disorders was 77.1% (4). Previous research reported that pain is the most common musculoskeletal symptom among nurses (5).

Intensive care units pose a high risk of musculoskeletal disorders in nurses. According to a study in China, almost all nurses in intensive care units reported work-related musculoskeletal problems, and approximately 30% of intensive care unit nurses requested a transfer to another unit or time off because of musculoskeletal problems (6).

Presenteeism is defined as a condition whereby employees perform activities in the workplace in a non-productive way and without putting in a good performance due to medical conditions and/or work-related problems (7). Workplace exposures and various health-related issues, including stress, allergies, upper respiratory tract infections and musculoskeletal pain,

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can cause presenteeism in nurses (8). In 2002, Koopman et al. (9) developed the Stanford Presenteeism Scale-6 (SPS-6), which evaluates the concept of presenteeism in the context of active commitment to work in the presence of health problems.

Work engagement is defined as a positive, fulfilling, affective-motivational state of work-related well-being (10). Work engagement is associated with satisfaction with the work being done (11). Work engagement can be measured using the Utrecht Work Engagement Scale (UWES). This scale has three important dimensions: willingness to work, work engagement and concentration on work. The 'willingness to work dimension' refers to the level of energy, enthusiasm and commitment to work. The 'work engagement dimension' relates to how individuals see their work (i.e. as having meaning and purpose). A high level of work engagement means employees are enthusiastic about their work and perceive it as inspiring. They are also proud of their work and evaluate it positively. The concentration on work dimension refers to the level of concentration of employees at work (12). They are not aware of time passing, thinking only of what they must do and being happy doing it (12).

Thus far, only one study has investigated the relationship between musculoskeletal pain and work engagement (13). This study found no relationship between the presence of musculoskeletal pain and work engagement in a crude analysis. However, in a subsequent analysis, the authors concluded that work engagement decreased in the presence of musculoskeletal pain when age, education time, body mass index (BMI), working hours and economic satisfaction values were taken into account (13). To our knowledge, no studies have investigated the relationship between musculoskeletal pain and work engagement among nurses. Therefore, the aim of our study was to evaluate the potential association of musculoskeletal pain with presenteeism and work engagement in intensive care unit nurses. The secondary aims of this study were to evaluate whether there was a relationship between occupational ergonomic exposures and musculoskeletal problems in the study population.

MATERIAL AND METHOD

The study were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and in line with the Strengthening the Reporting of Observational Studies in Epidemiology statement (14). The study was carried out with the permission of Necmettin Erbakan University Meram Faculty of Medicine Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 17.04.2020, Decision No: 2020/2420).

Study Design and Setting

The study was performed between Mar 2020 and August 2020 in Konya Research and Training Hospital. This was a nationwide, cross-sectional study on the association of musculoskeletal pain with work engagement and presenteeism in nurses working in intensive care units. We also evaluated the relationship between ergonomic exposures and the presence of chronic musculoskeletal pain.

Participants

The study population comprised nurses aged 18–55 years who had worked for at least 1 year in intensive care units in Turkey. In order to avoid gender discrimination, no data on gender were collected. Pregnant nurses, in addition to nurses with a BMI over 35, chronic inflammatory diseases, cancer or a history of spine stabilization surgery, joint arthroplasty and acute or chronic osteomyelitis, were excluded from the study. A pilot study was performed with 10 nurses who worked in Konya Training and Research Hospital surgery clinics.

After corrections based on the pilot study, the questionnaire was disseminated via email to members of the Turkish Society of Critical Care Nurses using the Google Forms© survey system. The database of the society hosts the email addresses of approximately 500 nurses. The questionnaire was also distributed to intensive care unit nurses in our hospital who fulfilled the inclusion criteria. Completion of the questionnaire was voluntary, and anonymity was guaranteed, with no names for personal data required.

Variables and Outcomes

Demographic and work/occupational characteristics (total time in the job, working duration in the intensive care unit, monthly working hours and shift type) of the study group were collected. In addition, all the participants completed the Brief Pain Inventory Short Form (BPI SF), a revised version of the Occupational Safety and Health Administration (OSHA) Ergonomic Assessment Checklist, the UWES-17 and the SPS-6. The presence of chronic pain was determined using a Google Form© survey designed specifically for the study.

The BPI SF is an easy-to-understand short pain assessment that a participant can complete alone. The BPI SF consists of two subscales evaluating pain intensity and pain-related effects. On the form, individuals are asked to evaluate their current pain, as well as the least and most severe pain in the last 24 hours and their average pain level. A numerical rating scale (0–10) is used to rate the severity of pain on the BPI SF, where 0 denotes 'no pain' and 10 denotes 'the most severe

pain ever experienced'. To evaluate the effect of pain on work-related parameters and daily activities of living, mood, sleep quality, mobility and social relationships were evaluated using a 0–10 numerical scale, where 0 indicated 'not affected at all' and 10 denoted 'totally affected' (15).

Pain is usually regarded as chronic when the pain recurs or lasts for more than 3–6 months (16). In our study, in assessing the presence of chronic musculoskeletal system pain, we used a cut-off value of 3 months as a reference. Those with chronic pain noted the site of pain on the first section of the BPI SF.

For the assessment of musculoskeletal exposures, we used a revised version of the OSHA Ergonomic Assessment Checklist Form, adapted for use with intensive care nurses (17). The checklist consisted of the following questions: Do you frequently lift 10 kg and/or occasionally 25 kg or more? Do you work 1–3 hours a day in jobs that require extreme reach points? Do you sit or work 1–3 hours in a standing position at workstations with an abnormal height (extremely low or extremely high)? Do you often move patients (care, lift, transfer from bed to bed, turning over in bed)? Do you often push patient stretchers or wheelchairs? Do you work at least 1–3 hours a day in jobs that require abnormal neck, waist/hip, elbow, wrist or shoulder postures and that place excessive force on these joints? The participants were asked to respond to these questions by writing yes or no.

Work engagement was assessed using the previously validated Turkish version of the UWES-17, (18). This is a self-report scale, which is scored using a 5-point Likert rating scale: 1 (strongly disagree) to 5 (strongly agree). Using this scale, vigour is assessed using 6 items, and dedication and absorption are assessed using 5 and 6 items, respectively (19).

Presenteeism was evaluated using the Turkish version of the SPS-6, validated by Coskun (20). The SPS-6 evaluates cognitive, behavioural and emotional status during working hours. The SPS-6 is scored between 6 and 30, with low scores denoting low job performance and high scores indicating good job performance (9).

Statistical Analysis

Statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY). There were no missing data on the variables in the study. The Shapiro–Wilk test was used to evaluate the distribution of the data. Descriptive data are presented as the median, with the interquartile range (IQR) for non-normally distributed numerical variables and as the frequency (n) and percentage (%) for categorical variables. A chi-square test was used to compare nominal variables between independent groups. Spearman's correlation analysis was used to evaluate the correlation between numerical and ordered categorical variables. The Mann–Whitney U test was employed to compare linear variables between independent groups. A value of $p < 0.05$ was considered statistically significant.

RESULTS

In total, 175 questionnaires were collected from the database survey and the intensive care nurses in our hospital. After excluding invalid questionnaires and questionnaires from respondents who did not fulfil the inclusion criteria, there were 153 questionnaires included in the study. **Table 1** shows the demographics of the nurses included in the study.

Table 1. Demographics and occupational characteristics of nurses

Variables	Median	IQR (25-75%)
Age (years)	31	28-40
Body mass index (kg/m2)	24.16	20.90-27.32
Total years in nursing profession	9	6-15
Years in the ICU	6	3-10
Monthly working hours	176	168-176

IQR= Interquartile Range; ICU= Intensive Care Unit

The results showed that 57.5% (n=88) were married, and 85% (n=130) had no chronic illnesses. The average working duration in the nursing profession was 9 years, and the average working duration in intensive care was 6 years. In the study population, 66.7% (n=102) of the nurses worked a shift system (night shift), and their monthly working hours were 176 hours on average. Chronic musculoskeletal pain was present in 76.5% (n=117) of the nurses, with the site of pain in the axial area (29%), extremities (16%) and axial area and extremities (61%).

According to the occupational musculoskeletal exposure assessment using the OSHA Ergonomic Assessment Checklist, the exposures were: lifting heavy weights (n=94, 61.4%), excessive reaching (n=66, 43.1%), transferring patients (n=103, 67.3%) and pushing patient stretchers or wheelchairs (n=59, 38.6%). The nurses were involved in jobs that required abnormal postures that placed excessive strain on their necks (52.9%, n=81), waists/hips (66%, n=101), elbows (44.4%, n=68), wrists (54.2%, n=83) and shoulders (56.2%, n=86). The results obtained from the scales related to musculoskeletal system pain (BPI SF), work engagement (UWES-17) and presenteeism (SPS-6) are given in **Table 2.**

Table 2. The Results of UWES, SPS-6 and BPI-SF scales

Scales	Median	IQR (25-75%)
BPI SF severity	3.25	0.5-4.5
BPI SF interference	2.57	0.21-4.57
SPS-6	19	18-23
UWES Vigor	3.17	2.20-4.40
UWES dedication	3.80	2.60-4.40
UWES absorption	3.17	2.33-3.83
UWES total	3.23	2.41-3.88

IQR= Interquartile Range; BPI SF= Brief Pain Inventory Short Form; BPI SF severity: Brief Pain Inventory Short Form pain severity subscale score; BPI SF interference: Brief Pain Inventory-Short Form pain interference subscale score; UWES: Utrecht Work Engagement Scale; SPS-6: Stanford Presenteeism Scale-6.

In the occupational musculoskeletal exposure evaluation using the OSHA Ergonomic Assessment Checklist, there was no statistically significant association between musculoskeletal exposure and the presence of chronic musculoskeletal pain. There was also no statistically significant difference between nurses with and without chronic musculoskeletal pain in terms of age, BMI, total years in the nursing profession, working years in intensive care units, monthly working hours and having a non-musculoskeletal chronic illness (p=0.33, 0.71, 0.92, 0.45, 0.64 and 0.29, respectively).

There was no statistically significant difference between nurses with and without chronic musculoskeletal pain in terms of work engagement and presenteeism when analysed using the UWES-17 subscales (vigour, dedication, absorption and total scores) and SPS-6 (p=0.33, 0.91, 0.81, 0.85 and 0.89, respectively).

There was no correlation between musculoskeletal pain severity and work engagement according to the total scores on the UWES-17 for vigour, dedication and absorption (p=0.09, 0.71 and 0.79, respectively). There was no correlation between musculoskeletal pain interference and dedication scores, absorption scores and total scores on the UWES-17 (p=0.32, 0.81 and 0.82, respectively), but a weak negative correlation was found between the BPI SF pain interference subscale and vigour subscale of the UWES-17 (p=0.04, r =-.166). In addition, no correlation was found between the BPI SF pain severity subscale and the SPS-6 (p=0.114, r=-.150), but a weak negative correlation was found between the pain interference subscale (BPI SF) and the SPS-6 (p=0.04, r=-.193).

DISCUSSION

Intensive care nursing requires both physical and mental dedication, as well as a high level of skill and effort. The relationship between occupational musculoskeletal exposures and musculoskeletal system pain and presenteeism and decreased work engagement among intensive care nurses has not been extensively studied. In this study, chronic musculoskeletal pain was present in 76.5% of the intensive care nurses. There was no difference in presenteeism, work engagement, occupational musculoskeletal exposure, working life and demographic data between the group with chronic musculoskeletal pain and those without.

In a study by Ceder et al. (13) on 702 nurses, 86% and 77% of nurses reported musculoskeletal pain and chronic musculoskeletal pain, respectively, in the last year, and age and BMI were higher in those with musculoskeletal pain. Ceder et al. (13) showed that musculoskeletal pain alone was not associated with work engagement. However, after adjustment for age, education years, BMI, working hours and financial satisfaction the difference between the groups was statistically significant. The insufficient number of cases in our study means we were unable to establish a direct causal relationship between pain and work engagement.

In our study, we evaluated the severity of chronic musculoskeletal pain and the impacts of pain on activities of daily living using the BPI SF. We found that musculoskeletal pain-related impacts on life determined using the BPI SF had a negative impact on vigour in work engagement, as assessed by the UWES-17. In a longitudinal study on 8,837 workers, Leijten et al. (21) evaluated physical health using SF-12 and work engagement using the UWES. They reported that higher work engagement was associated with better physical health. Ceder et al. (13) also reported that work engagement was negatively affected by the impacts of moderate and severe pain impact measured using the Örobro Musculoskeletal Pain Questionnaire. In our study, only pain interference was correlated with vigour. This may be explained by a potential bias effect of the item 'emotional state' on work engagement, which was not evaluated in our study.

In our study, we evaluated work engagement using the UWES-17. The vigour score (3.17) was low, and dedication (3.80), absorption (3.17) and work engagement total scores (3.23) were average. Similar to our study, Mason et al. (22) assessed work engagement among surgical intensive care unit trauma nurses using a 9-item UWES. They reported a score of 3.8, which is considered low.

The overall SPS-6 score in our study group was 19.0, which is considered moderate presenteeism. There was no correlation between musculoskeletal pain intensity and presenteeism in our study. In contrast, Bae et al. (23) showed that work-related musculoskeletal pain and presenteeism were related in their study on physiotherapists.

In our study, there was no correlation between occupational musculoskeletal exposure and the

presence of chronic musculoskeletal pain. However, in their study on 8,837 nurses, Leijten et al. (21) found that higher physical occupational exposure was associated with poorer physical health. Ando et al. (24) evaluated occupational musculoskeletal exposures and injuries in 314 nurses and found no association between neck, shoulder or arm pain and low back pain in the last month and occupational exposures in a Cox regression model. In a multi-centre study on nursing technicians and auxiliaries that employed the Nordic Musculoskeletal Questionnaire, Fonseca et al. (25) demonstrated that musculoskeletal disorders affecting the lower back, neck, shoulders and upper back were related to lifting, improper back postures and repetitive gestures. In a cohort study, Burdorf and Jansen (26) showed that work-related physical load was associated with the occurrence of low back pain and pain-related disability. The inconsistency of the findings of our study with those in the literature may be related to the subjective assessment of occupational musculoskeletal exposures in the current study. It may be possible to obtain more accurate results with researcher-based and detailed repetitive measurements of occupational exposure assessments.

Limitations

There are a few limitations in the present study. First, the low number of participants limits the generalizability of our results. Second, the voluntarily enrolment in the study may have caused selection bias, as those who volunteered to take part in the study may have been more likely than those who did not volunteer to suffer from musculoskeletal pain. Another limitation is the lack of any psychosocial evaluation. Work engagement is related to both work- and personal-related attributes, and psychosocial status may affect the relation between musculoskeletal pain and work engagement. This study did not include the effect of COVID-19 pandemic, because at the time of the questionnaire only the nurses at dedicated hospitals were dealing with COVID-19 patients, who were not included in this study.

CONCLUSION

Chronic musculoskeletal pain is common among intensive care nurses. In this study, work engagement and presenteeism were moderate. Chronic musculoskeletal system pain and pain intensity were not correlated with work engagement and presenteeism. Musculoskeletal pain-related impacts on daily activities of living have a negative effect on presenteeism and vigour in work engagement. We found no correlation between occupational musculoskeletal exposures and the presence of chronic musculoskeletal pain.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Necmettin Erbakan University Meram Faculty of Medicine Non-Pharmaceutical and Medical Device Research Ethics Committee (Date: 17.04.2020, Decision No: 2020/2420).

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

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REFERENCES

1. Menzel NN. Underreporting of musculoskeletal disorders among health care workers: research needs. AAOHN J 2008; 56: 487-94.
2. Motacki K, Motacki LM. Safe patient handling and movement in a pediatric setting. Pediatr Nurs 2009; 35: 221-5.
3. Tezel A. Musculoskeletal complaints among a group of Turkish nurses. Int J Neurosci 2005; 115: 871-80.
4. Karahan A, Kav S, Abbasoglu A, Dogan N. Low back pain: prevalence and associated risk factors among hospital staff. J Adv Nurs 2009; 65: 516-24.
5. Ribeiro NF, Fernandes Rde C, Solla DJ, Santos Jr AC, Sena Jr AS. Prevalence of musculoskeletal disorders in nursing professionals. Rev Bras Epidemiol 2012; 15: 429-38.
6. Yang S, Lu J, Zeng J, Wang L, Li Y. Prevalence and risk factors of work-related musculoskeletal disorders among intensive care unit nurses in China. Workplace Health Saf 2019; 67: 275-87.
7. Hemp P. Presenteeism: at work-but out of it. Harv Bus Rev 2004; 82: 49-58.
8. Mosteiro-Diaz MP, Baldonedo-Mosteiro M, Borges E, et al. Presenteeism in nurses: comparative study of Spanish, Portuguese and Brazilian nurses. Int Nurs Rev 2020; 67: 466-75
9. Koopman C, Pelletier KR, Murray JF, et al. Stanford presenteeism scale: health status and employee productivity. J Occup Environ Med 2002; 44: 14-20.
10. Schaufeli W, Maslach C, Marek T. Professional burnout: recent developments in theory and research. Washington, DC: Taylor & Francis; 1993. (Series in Applied Psychology).
11. Karoly P, Ruehlman LS, Okun MA. Psychosocial and demographic correlates of employment vs disability status in a national community sample of adults with chronic pain: toward a psychology of pain presenteeism. Pain Med 2013; 14: 1698-707.
12. Hakanen JJ, Bakker AB, Schaufeli WB. Burnout and work engagement among teachers. Journal of School Psychology 2006; 43: 495-513.
13. Malmberg-Ceder K, Haanpaa M, Korhonen PE, Kautiainen H, Soinila S. Relationship of musculoskeletal pain and well-being at work - Does pain matter? Scand J Pain 2017; 15: 38-43.
14. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370: 1453-7.

15. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap 1994; 23: 129-38.
16. Merskey H, Bogduk N, International Association for the Study of Pain. Task Force on Taxonomy. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. 2nd ed. Seattle: IASP Press; 1994.
17. OSHA. Ergonomic Assessment Checklist [1/4/2021]. Available from: https://www.osha.gov/ sites/default/files/2018-12/fy14_sh-26336-sh4_Ergonomic-Assessment-Checklist.pdf
18. Gunduz B, Capri B, Gokcakan Z. Examining of the relationships between professional burnout, work engagement and job satisfaction. J Educ Sci Res 2013; 3: 29-49.
19. Wilmar Schaufeli AB. UTRECHT Work Engagement Scale Netherlands: Utrecht University; 2004 [cited 2021 08/09/2021]. Available from: https://www.wilmarschaufeli.nl/ publications/ Schaufeli/Test%20Manuals/Test_manual_UWES_English.pdf
20. Coşkun O. İki işyerinde işe devamsızlık ve kendini işe verememede etkili faktörlerin değerlendirilmesi: Ankara University; 2012.
21. Leijten FR, van den Heuvel SG, van der Beek AJ, Ybema JF, Robroek SJW, Burdorf A. Associations of work-related factors and work engagement with mental and physical health: a 1-year follow-up study among older workers. J Occup Rehabil 2015; 25: 86-95.
22. Mason VM, Leslie G, Clark K, et al. Compassion fatigue, moral distress, and work engagement in surgical intensive care unit trauma nurses: a pilot study. Dimens Crit Care Nurs 2014; 33: 215-25.
23. Bae YH. Relationships between presenteeism and work-related musculoskeletal disorders among physical therapists in the Republic of Korea. Int J Occup Saf Ergon 2018; 24: 487-92.
24. Ando S, Ono Y, Shimaoka M, et al. Associations of self-estimated workloads with musculoskeletal symptoms among hospital nurses. Occup Environ Med 2000; 57: 211-6.
25. Fonseca Nda R, Fernandes Rde C. Factors related to musculoskeletal disorders in nursing workers. Rev Lat Am Enfermagem 2010; 18: 1076-83.
26. Burdorf A, Jansen JP. Predicting the long-term course of low back pain and its consequences for sickness absence and associated work disability. Occup Environ Med 2006; 63: 522-9.

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Evaluation of the health performances of the regions affiliated to the the ministry of health by multi-criteria decision making techniques

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ABSTRACT

Aim: The aim of this study is to determine the health performances of the regions in the 2019 Health Statistics Yearbook by using multi-criteria decision making techniques.

Material and Method: The study is a cross-sectional study and the data used in the study were obtained from the Ministry of Health Statistics Yearbook 2019. The population of the study consists of 12 regions (Western Anatolia, Western Black Sea, Eastern Black Sea, Eastern Black Sea, Eastern Marmara, Aegean, Istanbul, Central Anatolia, Mediterranean, Northeastern Anatolia, Western Marmara, Southeastern Anatolia, and Central Anatolia) included in the 2019 Health Statistics Yearbook. No sample was selected, and all regions were included in the study. ENTROPY Method was used for weighting the criteria and TOPSIS Method was used for ranking the alternatives. A total of 11 criteria, including six benefit criteria (number of general practitioners per 100,000 people, number of specialists per 100,000 people, number of hospital beds per 10,000 people, number of nurses and midwives per 100,000 people, number of hemodialysis devices per million people, and number of MRI devices per million people) and 5 cost criteria (infant mortality rate, maternal mortality rate, population per family medicine unit, crude mortality rate, population per 112 emergency aid station) were evaluated. Analyses were performed in Microsoft Excel program.

Results: In the study, the three most effective criteria used to determine the health performances of the regions were respectively determined as maternal mortality rate (28.68%), population per 112 emergency aid stations (17.43%), and crude death rate (15.63%). As a result of the analyzes of the TOPSIS Method, the five regions with the best health performance among the regions are Western Anatolia (0.68), Western Black Sea (0.66), Eastern Black Sea (0.65), Eastern Marmara (0.63), and Aegean (0.56) has been identified. While the average performance score of the regions is found as 0.53, Istanbul (0.51), Middle East Anatolia (0.50), Mediterranean (0.49), Northeast Anatolia (0.46), West Marmara (0.44), Southeastern Anatolia (0.40), and Central Anatolia (0.33) regions remained below this average.

Conclusion: The most important criteria in evaluating the health performances of regions are; maternal mortality rate, population per 112 emergency aid stations, and crude death rate. The regions with the best health performance are Western Anatolia, Western Black Sea and Eastern Black Sea. In order to improve the health performance of the regions, maternal mortality rate, crude death rate and population per family physician should be reduced.

Keywords: Multi-criteria decision making techniques, ENTROPY, health performance, TOPSIS

INTRODUCTION

Health services are one of the criteria showing the level of development of societies and are provided especially for the protection and promotion of health. With today's technological developments, the health literacy levels of societies have increased and these increases have led to rising costs of health services. Assessing the effectiveness of health services in a country is important in many ways. These include investments to be made in the region, cost control of health services, more efficient use of scarce resources and fair and equal assignment of health workforce in the country (1,2). Comparing the health performance of countries and planning health services in more detail and in a better way are among the most important issues that make identifying general problems in the field of health and evaluating the effectiveness of health services important (3). Among the 13 goals set by the United Nations to improve health indicators are

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objectives such as reducing maternal mortality, reducing infant mortality and combating infectious diseases (4).

In Turkey, as a result of the implementation of the Health Transformation Program (HTP) in 2003, significant progress and improvements have been achieved in the field of health. However, in addition to all these advances and improvements, when the health performance of the regions is analyzed, it is concluded that there are still inequalities of opportunity. Turkey's population and the need for health personnel are increasing day by day in parallel with each other. Taking the necessary steps in response to this increase is only possible through an assessment of the health regions in Turkey (5).

The main criteria used to make comparisons between the health levels of countries, regions and provinces are a number of criteria such as mortality, morbidity, fertility and health personnel (6). In addition to these, measures such as the number of beds, number of devices, etc. have also been used quite frequently and have gained an important place in the comparison of health performances. Especially in the literature, it is stated that maternal mortality rate and infant mortality rate are the most important measures of the socio-economic status of a society (7). Determining health performance by analyzing health indicators helps countries to learn the factors affecting health and the effectiveness of health services provided in the country (8).

Nowadays, multi-criteria decision-making techniques are used in situations where alternatives need to be compared according to certain criteria. These methods, which have recently started to be used especially in the field of health, are utilized in situations where multiple alternatives or one alternative needs to be evaluated according to more than one criterion (9).

In this study, it is aimed to determine the health performance of the regions, which are in Health Statistics Yearbook 2019 of the Republic of Turkey Ministry of Health, through multi-criteria decision-making techniques. ENTROPY Method and TOPSIS Method, which are multi-criteria decision making techniques, were used in the study. The main purpose of the study is to determine the health performance of the regions according to certain criteria and to be included in the health strategies to be implemented in the future.

In the method part of the study, the ENTROPY and TOPSIS methods used in the study were explained, the results in the study were given in the results part, and the results of the study were compared with the results of other studies in the literature in the discussion part.

MATERIAL AND METHOD

The study was carried out in accordance with the Declaration of Helsinki. Ethics committee approval is not required since the study was not conducted on humans and animals and secondary data were used.

The study is a cross-sectional study and the data used in the study were obtained from the Ministry of Health Statistics Yearbook 2019. The population of the study consists of 12 regions (Western Anatolia, Western Black Sea, Eastern Black Sea, Eastern Black Sea, Eastern Marmara, Aegean, Istanbul, Central Anatolia, Mediterranean, Northeastern Anatolia, Western Marmara, Southeastern Anatolia, and Central Anatolia) included in the 2019 Health Statistics Yearbook. No sample was selected, and all regions were included in the study. ENTROPY Method was used for weighting the criteria and TOPSIS Method was used for ranking the alternatives. A total of 11 criteria, including six benefit criteria (number of general practitioners per 100,000 people, number of specialists per 100,000 people, number of hospital beds per 10,000 people, number of nurses and midwives per 100,000 people, number of hemodialysis devices per million people, and number of MRI devices per million people) and 5 cost criteria (infant mortality rate, maternal mortality rate, population per family medicine unit, crude mortality rate, population per 112 emergency aid station) were evaluated. The criteria used in the study were determined as a result of the literature review and were finalized with the opinions of three experts. Analyses were performed in Microsoft Excel program.

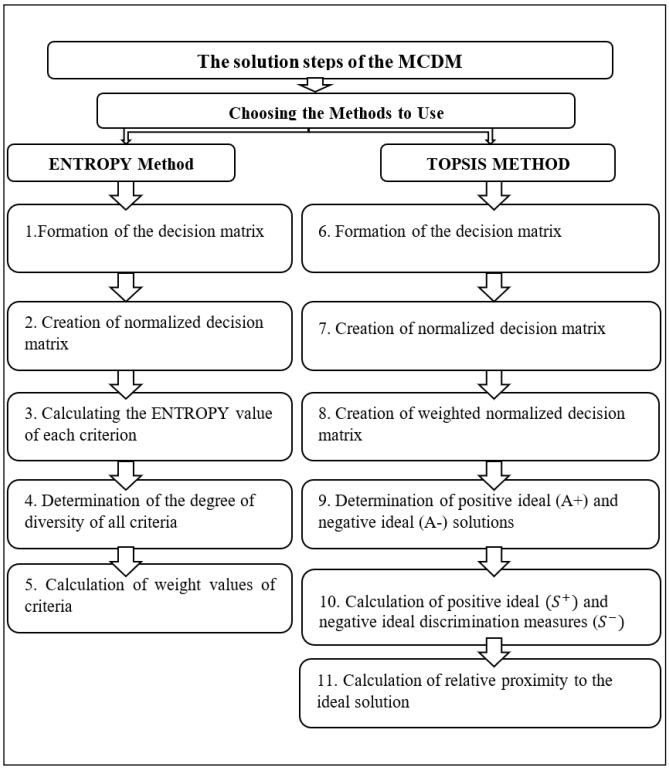

Figure 1. The solution steps of the MCDM

ENTROPY Method

The ENTROPY method consists of creating the initial decision matrix, creating the normalized decision matrix, calculating the ENTROPY value of each criterion, determining the degree of diversity of all criteria and calculating the weight values of the criteria. The analysis methods of these stages are as follows (10-12).

1. Formation of the Decision Matrix: It is a matrix representing m number of alternatives and n number of criteria. Xij in the matrix indicates the value of alternative i according to criterion j.

$$D=\begin{bmatrix} X_{11} & X_{12} & X_{13} & \dots & X_{1j} & \dots & X_{1n} \\ X_{21} & X_{22} & X_{23} & \dots & X_{2j} & \dots & X_{2n} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ X_{i1} & X_{i2} & X_{i3} & \dots & X_{ij} & \dots & X_{in} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ X_{m1} & X_{m2} & X_{m3} & \dots & X_{mj} & \dots & X_{mn} \end{bmatrix} \quad (1)$$

2. Creation of Normalized Decision Matrix: A normalized decision matrix (R Matrix) is created by normalizing with the formula below.

$$r_{ij} = x_{ij} / \sum_{i=1}^{m} x_{ij}$$

$$R=\begin{bmatrix} R_{11} & R_{12} & R_{13} & \dots & R_{1j} & \dots & R_{1n} \\ R_{21} & R_{22} & R_{23} & \dots & R_{2j} & \dots & R_{2n} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ R_{i1} & R_{i2} & R_{i3} & \dots & R_{ij} & \dots & R_{in} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ R_{m1} & R_{m2} & R_{m3} & \dots & R_{mj} & \dots & R_{mn} \end{bmatrix} \quad (2)$$

3. Calculating the ENTROPY Value of Each Criterion: The ENTROPY values of each criterion are calculated using the formula below. The number k in the formula is obtained by the formula 1/lnm.

$$e_j = -k / \sum_{i=1}^{m} r_{ij} \ln r_{ij} \quad (3)$$

4. Determination of the Degree of Diversity of All Criteria: The degree of diversity of each criterion is calculated with the help of the following formula.

$$d_j = 1 - e_j \quad (4)$$

5. Calculation of Weight Values of Criteria: The weights of all criteria are calculated using the formula below. The important point here is that the sum of the weights of all criteria should be equal to 1.

$$w_j = d_j / \sum_{j=1}^{n} d_j \quad (5)$$

TOPSIS Method

The TOPSIS method consists of the following stages: construction of the initial decision matrix, construction of the normalized decision matrix, construction of the weighted normalized decision matrix, determination of the positive ideal and negative ideal solutions, calculation of the positive ideal and negative ideal separation measures and calculation of the relative proximity to the ideal solution. The analysis methods of these stages are shown below (13-15).

1. Formation of the Decision Matrix: It is a matrix representing m number of alternatives and n number of criteria. The aij in matrix indicates the value of alternative i according to criterion j.

$$A=\begin{bmatrix} a_{11} & a_{12} & a_{13} & \dots & a_{1j} & \dots & a_{1n} \\ a_{21} & a_{22} & a_{23} & \dots & a_{2j} & \dots & a_{2n} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ a_{i1} & a_{i2} & a_{i3} & \dots & a_{ij} & \dots & a_{in} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ a_{m1} & a_{m2} & a_{m3} & \dots & a_{mj} & \dots & a_{mn} \end{bmatrix} \quad (6)$$

2. Creation of Normalized Decision Matrix: The data are normalized using the formula below and the Normalized Decision Matrix (R Matrix) is generated

$$r_{ij} = a_{ij} / \sqrt{\sum_{i=1}^{m} a_{ij}^2}$$

$$i = 1,2,3,4 \dots\dots, m$$

$$j = 1,2,3,4 \dots\dots, n$$

$$R=\begin{bmatrix} r_{11} & r_{12} & r_{13} & \dots & r_{1j} & \dots & r_{1n} \\ r_{21} & r_{22} & r_{23} & \dots & r_{2j} & \dots & r_{2n} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ r_{i1} & r_{i2} & r_{i3} & \dots & r_{ij} & \dots & r_{in} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ r_{m1} & r_{m2} & r_{m3} & \dots & r_{mj} & \dots & r_{mn} \end{bmatrix} \quad (7)$$

3. Creation of Weighted Normalized Decision Matrix: The weights of the criteria are calculated with one of the criterion weighting methods and the values obtained are multiplied by each value in the normalized decision matrix. While the weighted normalized value is denoted with vij, the weight value is denoted with wj.

$$V=\begin{bmatrix} w_1r_{11} & w_2r_{12} & w_3r_{13} & \dots & w_jr_{1j} & \dots & w_nr_{1n} \\ w_1r_{21} & w_2r_{22} & w_3r_{23} & \dots & w_jr_{2j} & \dots & w_nr_{2n} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ w_1r_{i1} & w_2r_{i2} & w_3r_{i3} & \dots & w_jr_{ij} & \dots & w_nr_{in} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ w_1r_{m1} & w_2r_{m2} & w_3r_{m3} & \dots & w_jr_{mj} & \dots & w_nr_{mn} \end{bmatrix} \quad (8)$$

4. Determination of Positive Ideal (A+) and Negative Ideal (A-) Solutions: Ideal and Negative ideal solution points are determined. If the criterion evaluated is the utility criterion, the positive ideal solution consists of

the best values of V and the negative ideal solution consists of the worst values. If the evaluated criterion is the cost criterion, the positive ideal solution consists of the smallest value of V, while the negative ideal solution consists of the largest value. The following formulas are used to calculate the ideal solutions.

$$A^+ = (v_1^+, v_2^+, v_3^+, \ldots, v_n^+)$$

$$A^+ = \{(\max_j v_{ij} \setminus j \in J), (\min_j v_{ij} \setminus j \in J')\}$$

$$A^- = (v_1^-, v_2^-, v_3^-, \ldots, v_n^-) \quad (9)$$

$$A^- = \{(\min_j v_{ij} \setminus j \in J), (\max_j v_{ij} \setminus j \in J')\}$$

In the formula, the benefit criterion is shown as J and the cost criterion is shown as J'.

5. Calculation of Positive Ideal (S^+) and Negative Ideal Discrimination Measures (S^-): Discrimination measures are a calculation between alternatives and follow a mathematical formula called Euclidean distances. This separation is based on the previous step of the TOPSIS method. The distance of each alternative from the positive-ideal and negative-ideal solution is calculated with the following formulas.

$$S^+ = \sqrt{\sum_{j=1}^{n} (v_{ij} - v_i^+)^2}$$

$$S^- = \sqrt{\sum_{j=1}^{n} (v_{ij} - v_i^-)^2} \quad (10)$$

$$i = 1,2,3,\ldots, m$$

6. Calculation of Relative Proximity to the Ideal Solution: C_i^* in the formula is between $0 \leq C_i^* \leq 1$ After these calculations, the alternative closest to 1 is the most successful alternative, and the alternatives are ranked in descending order of success

$$C_i^* = \frac{S_i^-}{S_i^- - S_i^+}$$

$$i = 1,2,3,\ldots, m \quad (11)$$

Table 1. Criteria used in this study

Criteria Code	Criteria
K1	Number of general practitioners per 100,000 people*
K2	Number of Specialist Physicians per 100,000 people*
K3	Number of hospital beds per 10,000 people*
K4	Number of Nurses and Midwives per 100,000 people*
K5	Number of actually used hemodialysis devices per million people*
K6	Number of MRI devices per million people*
K7	Infant mortality rate**
K8	Maternal Mortality Rate**
K9	Population per family medicine unit**
K10	Crude Mortality Rate**
K11	Population Per 112 Emergency Aid Station**

*Benefit Criterion
**Cost Criterion

The criteria used in the study were determined as a single score at the end of the study, thus enabling the regions to be ranked according to their performance (**Table 1**).

RESULTS

The initial decision matrix in **Table 2** was created using Health Statistics Yearbook 2019 of the Republic of Turkey Ministry of Health. The initial decision matrix is used in both the ENTROPY method and the TOPSIS method in studies where weights are based on the ENTROPY method and ranking is based on the TOPSIS method (**Table 2**).

To determine the weights of the criteria evaluated in the study, the stages of the ENTROPY method were applied, and the criteria weights determined as a result of the analyzes are shown in **Table 3**. According to the results of the study, the three most effective criteria used in determining the health performance of the regions are maternal mortality rate (28.68%), population per 112 emergency aid station (17.43%) and crude mortality rate (15.63%) (**Table 3**).

Using the initial decision matrix in **Table 2**, the Si+, Si- and Ci values of the regions were determined as a result of the application of the stages of the TOPSIS method and these values are shown in **Table 4**.

The health performance ranking of the regions according to TOPSIS is shown in **Table 5.**

As a result of the analysis of TOPSIS method, the five regions with the most successful health performance among the regions are West Anatolia (0.78), West Black Sea (0.66), East Black Sea (0.65), East Marmara (0.63) and Aegean (0.56). While the average performance score of the regions was 0.54, Istanbul (0.51), Central Anatolia (0.50), Mediterranean (0.49), Northeast Anatolia (0.46), West Marmara (0.44), Southeast Anatolia (0.40) and Central Anatolia (0.33) regions were below this average.

Table 2. Initial decision matrix

Initial Decision Matrix											
Regions	**Criteria**										
	K1	**K2**	**K3**	**K4**	**K5**	**K6**	**K7**	**K8**	**K9**	**K10**	**K11**
Southeast Anatolia	61	63	23.3	254	128.6	8.7	13.5	18	3155	9.2	30323
Middle East Anatolia	67	70	30.5	326	161.1	10.2	11.5	15.9	3105	8.4	20686
Northeast Anatolia	75	72	29.6	313	171.4	9.1	10	17.3	2953	12.1	20000
Central Anatolia	62	81	31	335	274.1	9.6	9.9	24.4	3039	15.3	19785
Mediterranean	58	95	28.7	310	228	12	8.8	14.7	3100	13.8	30106
Aegean	57	114	29	315	256.9	10.6	8	11.7	3161	21.4	29414
Western Black Sea	67	82	32.6	351	294.7	8.6	7.4	10.1	3107	17.7	19124
Western Anatolia	51	145	33.9	349	223.6	12.7	7.3	2.9	3236	16.1	33162
West Marmara	57	90	29.5	325	230.7	10.8	7.3	15.8	3135	25.5	23542
Istanbul	46	136	26.2	264	178.8	12.3	7.1	11.1	3123	16.1	50551
East Marmara	52	92	26.2	297	222.5	10.1	7	8.5	3241	20.8	32115
Eastern Black Sea	68	87	32.9	372	268	11.2	5.9	10.2	3154	20.7	16013

Table 3. ENTROPY method weighting and ratios of criteria

Criteria	**K1**	**K2**	**K3**	**K4**	**K5**	**K6**	**K7**	**K8**	**K9**	**K10**	**K11**
Ej Value	0.99648	0.98709	0.99793	0.99781	0.9898	0.99684	0.98865	0.96588	0.99988	0.9814	0.97927
Diversity (dj)	0.00352	0.01291	0.00207	0.00219	0.0102	0.00316	0.01135	0.03412	0.00012	0.0186	0.02073
Criteria Weights wj	0.0296	0.10853	0.01737	0.01841	0.08575	0.02657	0.09538	0.2868	0.00097	0.15632	0.17429
Criteria Weights wj (%)	2.96%	10.85%	1.74%	1.84%	8.57%	2.66%	9.54%	28.68%	0.10%	15.63%	17.43%

Table 4. Si+, Si- and Ci values of TOPSIS method alternatives

Regions	**SI+**	**SI-**	**CI**
Southeast Anatolia	0.09899	0.06685	0.4031
Middle East Anatolia	0.08229	0.08515	0.5085
Northeast Anatolia	0.08899	0.07723	0.4646
Central Anatolia	0.12758	0.06388	0.3337
Mediterranean	0.07637	0.07622	0.4995
Aegean	0.06681	0.08724	0.5663
Western Black Sea	0.05283	0.10486	0.665
Western Anatolia	0.03763	0.13436	0.7812
West Marmara	0.09003	0.07274	0.4469
Istanbul	0.08094	0.08635	0.5162
East Marmara	0.05740	0.10091	0.6374
Eastern Black Sea	0.05634	0.10678	0.6546

Table 5. Health performance ranking of regions in the Health Statistics Yearbook 2019

Item no.	**Regions**	**Performance Scores**
1.	West Anatolia	0.781
2.	West Black Sea	0.665
3.	East Black Sea	0.655
4.	East Marmara	0.637
5.	Aegean	0.566
	Region Average	0.540
6.	İstanbul	0.516
7.	Middle East Anatolia	0.509
8.	Mediterranean	0.499
9.	Northeast Anatolia	0.465
10.	West Marmara	0.447
11.	Southeast Anatolia	0.403
12.	Central Anatolia	0.334

DISCUSSION

In the study, the three most effective criteria used to determine the health performance of the regions were maternal mortality rate (28.68%), population per 112 emergency aid station (17.43%) and crude mortality rate (15.63%). As a result of the analysis of TOPSIS method, the five regions with the most successful health performance among the regions were identified as West Anatolia (0.78), West Black Sea (0.66), East Black Sea (0.65), East Marmara (0.63) and Aegean (0.56). While the average performance score of the regions was 0.54, Istanbul (0.51), Central Anatolia (0.50), Mediterranean (0.49), Northeast Anatolia (0.46), West Marmara (0.44), Southeast Anatolia (0.40) and Central Anatolia (0.33) regions were below this average.

Şantaş et al. (16) examined the health performance of statistical regions and concluded that the Western Anatolia Region has the best health performance, and the Southeastern Anatolia Region has the worst health performance. Although multi-criteria decision-making techniques were not used in this study by Şantaş et al., it is seen that it has a similar result with this study.

Öksüzkaya (17) used data envelopment analysis to analyze the health performance of statistical regions and found that the hospitals affiliated to the Ministry of Health in the Western Anatolia region were active .

Özdemir (18) also used the data envelopment analysis to analyze the health performance of the regions and concluded that West Anatolia, West Marmara and Aegean

regions are active only in terms of Banker, Charnes, Cooper (BCC) models.

CONCLUSION

Nowadays, multi-criteria decision-making techniques is being used in the field of health in various new subjects. However, there has not been any study in which the health performance of the regions classified according to the Classification of Statistical Region Units in the Annals of Health Statistics published by the Ministry of Health has been examined using the ENTROPY-based TOPSIS Method. While the study with this aspect has an original value, it also has the quality of setting an example for subsequent studies.

In the study, the most important criteria for evaluating the health performance of the regions were determined as maternal mortality rate, population per 112 emergency aid stations, and crude mortality rate. The regions with the best health performance were determined as West Anatolia, West Black Sea and East Black Sea regions. In order for the health performance of the regions to improve, the maternal mortality rate, the crude mortality rate, the population per 112 emergency aid stations, and the population per family physician should be reduced. With all these, it is recommended that the strategies in the West Anatolia Region, which is the best region in terms of health performance, be well analyzed and implemented in other regions so that other regions can have the same scores as the West Anatolia Region.

There is no person/organization that supports the study financially and the authors do not have any interest-based relationship

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval is not required since the study was not conducted on humans and animals and secondary data were used in the study.

Informed Consent: Since the study was not performed on patients, informed consent is not required.

Peer Review Process: Externally peer reviewed.

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

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REFERENCES

1. Eren H, Ömürbek N. Aggregation and analysis of performance in terms of Turkey's health indicators. Mehmet Akif Ersoy University Journal of Social Sciences Institute 2019; 11: 421-52.
2. Arslanhan S. How rising health expenditures affect key health indicators. TEPAV Evaluation Note. 2010.
3. Saygın ZÖ, Kundakçı N. Evaluation of OECD countries in terms of health indicators with EDAS and ARAS methods. Alanya Academic Review 2020; 4: 911-38.
4. United Nations. Global indicator framework for the Sustainable Development Goals and targets of the 2030 Agenda for Sustainable Development (Accessed September 20, 2021).
5. Tekin B. Grouping of cities in terms of primary health indicators in Turkey: an application of cluster analysis. Journal of the Faculty of Economics and Administrative Sciences 2015; 5: 389-416.
6. Sayılı U, Aksu Sayman Ö, Vehid S, Köksal SS, Erginöz E. Comparison of health indicators and health expenditures of Turkey and OECD countries. Online Turkish Journal of Health Sciences 2017; 2: 1-12.
7. Sonğur C. Cluster analysis of organization for economic cooperation and development countries according to health indicators. Journal of Social Security 2016; 6: 197-224.
8. First National Center. Understanding Health Indicators. Ottawa: National Aboriginal Health Organization, 2007.
9. Ömürbek N, Altın FG, Şimşek, A, Eren H. Evaluation of the efficiencies of the cities in terms of health indicators in Turkey using ENTROPY-based data envelopment Analysis. Süleyman Demirel University Visionary J 2021; 12: 16-45.
10. Akçakanat Ö, Eren H, Aksoy E, Ömürbek V. Performance evalualiton by ENTROPY and WASPAS methods at banking sector. The Journal of Faculty of Economics Administrative Scicences 2017; 22: 285-300.
11. Zou ZH, Yun Y, Sun JN. Entropy method for determination of weight of evaluating indicators in fuzzy synthetic evaluation for water quality assessment. J Environment Sci (China) 2006; 18: 1020–3.
12. Zhu Y, Tian D, Yan F. Effectiveness of entropy weight method in decision-making. Hindawi Mathematical Problems Engineering 2020. https://doi.org/10.1155/2020/3564835
13. Mohammed MA, Abdulkareem KH, Al-Wisy AS, et al. Benchmarking methodology for selection of optimal COVID-19 diagnostic model based on entropy and TOPSIS Methods. IEEE Access, 2020; 8: 99115-31.
14. Yong D. Plant location selection based on fuzzy TOPSIS. Int J Adv Manufact Technol 2006; 28: 839-44.
15. Zhang H, Gu CL, Gu LW, Zhang Y. The evaluation of tourism destination competitiveness by TOPSIS & information entropy—A case in the Yangtze River Delta of China. Tourism Management 2011; 32: 443-51.
16. Şantaş F, Şantaş G. The current situation and ranking of Turkey, regions and provinces in terms of health variables. Hitit J Soc Sci 2018; 11: 2419-32.
17. Öksüzkaya M. Examining the effectiveness among regions in the health sector. Gazi Üniversitesi Sosyal Bilimler Derg 2017; 4: 280-300.
18. Özdemir A. Measuring of healthcare service delivery efficiency of NUTS-1 territories in Turkey using data envelopment analysis. J Health Sci Adiyaman University 2020; 6: 231-42.

Original Article

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The effect of anal hygiene method in prevention from recurrent lower urinary tract infections in women

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ABSTRACT

Aim: To evaluate the effects stopping the use of water and hands on preventing urinary tract infections (UTI) for a group of female patients having recurrent UTIs (rUTI).

Material and Method: A retrospective observational study conducted in a tertiary care hospital between February 2017 and March 2018. 273 female patients which had rUTIs without any concomitant risk factors were included. In the study, 2 or more bacteriologically documented UTIs in the last 6 months were accepted as rUTI. The groups of the study defined as using their hands, using water only and using toilet paper (using either one of these two methods and then using toilet paper). Patients were observed for an average time of 10.4 months after stopping the use of water and hands for anal cleansing after defecation. Instead they were all given toilet education and started wiping for anal hygiene.

Results: There was a statistically significant relationship between previous history of UTI and washing with hands + water (p=0.021). The rate of previous UTIs were significantly higher in the group of patients using their hands for anal washing (69% vs 31%). No relation was found between previous UTI history variable for using toilet paper and flushing with water only (p>0.05). Our results showed a statistically significant decrease of UTIs after stopping the use of water and hands in the patient group who had a previous UTI history (p=0.001).

Conclusion: We managed to underline that washing with hands for anal cleansing as a risk factor for rUTIs in women. Also showed the positive effect of stopping the use of water and hands for anal cleansing after defecation for prevention from rUTIs. We encourage all clinicians for further studies to investigate this issue in the future.

Keywords: Recurrent urinary tract infections, anal cleansing, anal hygiene

INTRODUCTION

Recurrent lower urinary tract infections (rUTI) in women are a very common and troublesome condition around the world (1). Nearly 50% of all women will have at least one urinary tract infections (UTI) in their lifetime, with a recurrence rate about 25% (1,2). Hence the treatment and prevention is utmost significant for all clinicians. Although there are many predisposing factors, it is assumed that anal cleansing after defecation is an important one since the most common pathogens for UTIs are bowel flora bacteria with *Escherichia coli* (*E. coli*) being the most common among these (3).

The prevention from rUTIs in women has a wide range from surgical correction of underlying anatomical causes to the use of prophylactic antibiotics or other therapeutic agents. Behavioral treatments related to specific risk factors such as hygiene before and after sexual intercourse or increasing fluid intake has been well established but there is a scarcity of data about the anal region hygiene methods (4-10).

There are several studies in the literature investigating the possible causes of rUTIs such as sexual hygiene, hand sanitation, fluid intake or BMI, but to the best of our knowledge there is no study focusing on the anal cleansing methods in rUTI patients (11). Anal cleansing method is highly variable for different cultures. We particularly focused on one method in this study: anal cleansing with water.

There is an estimate of over 1 billion people using water and hands in different ways for anal hygiene after defecation. In many cultures, especially in Muslim

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and Hindu populations, water is usually used for anal cleansing using a jet, as with a bidet, or splashed and washed with the hand (12). In this study, we hypothesized that giving toilet hygiene education and also stopping the use of water and hands can be beneficial for a group of female patients having rUTIs. Findings from this study will highlight the etiological importance of anal hygiene method and outcomes associated this condition will influence future treatment guidelines and strategies in this particular group of patients.

MATERIAL AND METHOD

The study was carried out with the permission of Niğde Ömer Halisdemir University Hospital Noninvasive Clinical Researches Ethics Committee (Date:15.08.2022, Decision No:2022/90). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This is an observational and retrospective study with an analytical component.

Hospital information system records were scanned between 01 January 2017 and 31 June 2018. All patients who had rUTIs and anal hygiene method between 01 January 2017 and 31 June 2018 were included. All participants agreed to participate in this study and signed an informed consent form. There is a variety of definitions for recurrent urinary tract infections (rUTI) in the current literature (13). In this particular study, 2 or more bacteriologically documented UTIs in the last 6 months were accepted as rUTI. The study group comprised of 273 women over the age of 18 who had rUTIs and no other known predisposing factors. All patient groups were using water for anal cleansing. All patients required urinalysis and urine culture in the last 6 months. Patients whose urine culture results could not be reached were excluded from the study. The toilet habits of the patients included in the study were questioned and recorded. Anal or anal-to-vaginal sexual intercourse was questioned as a predisposing factor and these patients were excluded from the study. Patients who received cystoscopy or urodynamic examination indications were excluded from the study, considering that the culture results may develop contamination or infection due to the procedures. The patients in the group 'using their hands' were touching their perianal region or splashing the water with their hands for cleansing. The patients in the group 'using water only' were not doing any additional cleansing or drying method after washing with water. The patients in the group 'using toilet paper' were using either one of these two methods and then using toilet paper. Patients with complicating factors such as urinary stone disease, pregnancy, anatomical abnormality of the urinary tract, neurologic conditions, diabetes, or currently taking immunosuppression were excluded from the study.

Statistical Analysis

The normal distribution of data was tested with the Shaphiro-Wilk test. The numerical data were analyzed independently in two groups and Mann Whitney U test was used for those who did not show normal distribution. The relationships of two independent variables at the categorical level were tested with chi-square. In the two dependent groups, the relationship of the variables with each other was done by McNamer test and spearman correlation. The mean±standard deviation (Median) for numerical variables and the number and % values for categorical variables were given as descriptive statistics. IBM SPSS Windows 22.0 package program was used for statistical analysis and $p<0.05$ was considered statistically significant.

RESULTS

The number of documented UTIs for all patients varied between 2 and 7 (2.50±0.84) in the last 6 months and age 20 and age 94 (67.94±13.13) as shown in **Table 1**.

Table 1. Number of documented UTIs in the last 6 months

	Min	Max	Mean
Number of documented UTIs in last 6 months	2.0	7.0	2.5±0.8
Age	20	94	67.94±13.13

As this study was conducted with a group of Turkish females, the use of hands with water for anal cleansing was high. The most frequent causing pathogen was *E. coli*. The frequencies of different categorical variables are listed in **Table 2**.

Table 2. Frequencies of categorical variables

	Count	%
Using toilet paper		
No	175	64.1
Yes	98	35.9
Anal hygiene		
Flushing with water only	99	36.3
Washing with hands + water	174	63.7
Previous UTI history		
No	168	61.5
Yes	105	38.5
Urine culture		
E. coli	157	57.51
Klebsiella	27	9.89
Pseudomonas	25	9.16
Proteus	29	10.62
Staph	20	7.33
Other	15	5.49
UTI after stopping the use of water		
No	207	75.8
Yes	66	24.2

The relationship between the number of documented UTIs and the method of anal cleansing is summarized in **Table 3.** The use of toilet paper was not found to be a statistically significant variable for rUTIs (p=0.729). Similar results were observed for the groups of washing with hands + water and flushing with water only (p>0.05). p value was obtained from Mann Whitney U test.

Table 3. The relationship between the number of documented UTIs and anal cleansing method

	n	Mean±SD	Median	p
Using toilet paper				0.729
No	175	2.49±0.8	2	
Yes	98	2.51±0.91	2	
Anal hygiene				0.918
Flushing with water only	99	2.51±0.87	2	
Washing with hands+water	174	2.49±0.82	2	
Urine culture				0.787
E. coli	157	2.5±0.75	2	
Klebsiella	27	2.41±0.75	2	
Pseudomonas	25	2.44±0.96	2	
Proteus	29	2.48±1.09	2	
Staph	20	2.65±1.14	2	
Other	15	2.53±0.83	2	

There was a statistically significant relationship between previous history of UTI and washing with hands + water (p=0.021). The rate of previous UTIs were significantly higher in the group of patients using their hands for anal washing (69% vs 31%). No relation was found between previous UTI history variable for using toilet paper and flushing with water only (p> 0.05). These data are shown in **Table 4**.

Table 4. Previous History of UTIs and anal cleansing method

	Previous UTI history			
	Yes		No	
	n	%	n	%
Using toilet paper				
Yes	45	42.9	53	31.5
No	60	57.1	115	68.5
p=0.058				
Anal hygiene				
Washing with hands + water	116	69.0	58	55.2
Flushing with water only	52	31.0	47	44.8
p=0.021*				

There was a statistically significant decrease of UTIs after stopping the use of water in the patient group who had a previous UTI history (p=0.001; r=-0.123 p=0.042). **Table 5** shows this relationship.

Table 5. The effect of stopping water for the patients with a previous UTI history

	UTI after stopping the use of water		Total
	Yes	No	
Previous UTI history			
Yes			
n	17	88	105
% within	27.4%	41.7%	38.5%
No			
n	45	123	168
% within	72.6%	58.3%	61.5%
Total			
Count	62	211	273
% within	100.0%	100.0%	100.0%

DISCUSSION

For all the clinicians rUTIs in women are an increasing concern as this group of patients might cause unnecessary use of antibiotics and may lead to a higher prevelance of drug-resistant bacteria. Antibiotic resistance represents a major problem worldwide, mainly due to the lack of new drugs against carbapenemase-producing Enterobacteriaceae (14,15). Thus, prevention from rUTIs is a very important goal for both the patients with rUTIs and all population who are under the risk of facing an UTI in the future.

The preventative measures for rUTIs are well defined. Continuous antibiotic prophylaxis or postcoital prophylaxis, if there is close correlation with sexual intercourse, are most effective to prevent rUTIs. The European Association of Urology suggests behavioural modifications and non-antimicrobial measures as first line. Antimicrobial prophylaxis only after these methods have been attempted (16). In postmenopausal patients, vaginal use of oestriol can be effective (17,18). Oral or parenteral immunoprophylaxis can be tried for rUTI (19). Other choices of therapy are prophylaxis with cranberry products or some probiotics which lack solid scientific data (20).

On the other hand, there is a scarcity of data on the anal hygiene methods in the literature. To be more specific, to the best of our knowledge, there are no publications or guidelines concentrating on the different anal cleansing methods after defecation for the etiology of UTIs. This is specifically important for the clinicians working in countries which have Turkish, Muslim, Asian, European or Hindu populations. These populations may use water for anal cleansing with or without using their hands or toilet paper. As it is a widely accepted fact that most of the UTIs are caused by bowel flora bacteria, this way of contamination must be considered for those who have rUTIs.

Even we did not manage to show a direct relationship with using water for anal cleansing with rUTIs, our results suggested that the rate of previous UTIs were significantly more and the relapsing or recurring infections were

significantly less in the group of patients using their hands for anal cleansing. When the two statistically significant results combined, we reached a result suggesting that using hands with water for anal cleansing was a major risk factor for rUTIs and the behavioral modification to stop this habit improves the future risk of having UTIs.

Lack of randomization and the limited number of patients were the main limitations for our study. Furthermore, categorizing patients by only using water with their hands or toilet paper, can't be the only factor causing rUTIs. There also very important factors beyond our database such as the level of hand hygiene, cleanliness of the water used for washing, fluid intake habits or other predisposing factors such as post-coital infections and partner-related contaminations.

It is also supported by literature data that there is a serious relationship between recurrent urinary tract infections and bladder pain syndrome/interstitial cystitis. The effect of bladder pain syndrome/interstitial cystitis on quality of life and its relationship with urinary tract infections were also studied by Sarıkaya et al. (21). The study of Sarıkaya et al. and literature data also support our findings on urinary tract infections.

The limitation of our study is that the follow-up period of the patients was not very long and the European Society for the Study of Interstitial Cystitis (ESSIC) scores of the patients could not be performed. Quality of life questionnaires (O'Leary scale etc.) could not be applied because it is a retrospective study and because of the limitations in patients' ability to remember the past.

CONCLUSION

We managed to underline the positive effect of stopping the use of water and hands for anal cleaning after defecation for prevention from rUTIs. We encourage all clinicians for further studies to investigate this issue in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Niğde Ömer Halisdemir University Hospital Noninvasive/ Clinical Researches Ethics Committee (Date: 15.08.2022, Decision No: 2022/90).

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

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Foxman B. Recurring urinary tract infection: incidence and risk factors. Am J Public Health 1990; 80: 331-3.
2. Albertsen PC. Risk factors for recurrent urinary tract infection in young women. J Urol 2003; 170: 698.
3. Aydin A, Ahmed K, Zaman I, Khan MS, Dasgupta P. Recurrent urinary tract infections in women. Int Urogynecol J 2015; 26: 795-804.
4. Nickel JC. Practical management of recurrent urinary tract infections in premenopausal women. Rev Urol 2005; 7: 11-7.
5. Kodner CM, Thomas Gupton EK. Recurrent urinary tract infections in women: diagnosis and management. Am Fam Physician 2010; 82: 638-43.
6. Hickling, DR, Nitti VW. Management of recurrent urinary tract infections in healthy adult women. Rev Urol 2013; 15: 41-8.
7. Gupta K., Trautner BW. Diagnosis and management of recurrent urinary tract infections in non-pregnant women. BMJ 2013; 346: f3140.
8. Gupta K, Stamm WE. Pathogenesis and management of recurrent urinary tract infections in women. World J Urol 1999; 17: 415-20.
9. Eells SJ, Bharadwa K, McKinnell JA. Miller LG. Recurrent urinary tract infections among women: comparative effectiveness of 5 prevention and management strategies using a Markov chain Monte Carlo model. Clin Infect Dis 2014; 58: 147-60.
10. Al-Badr A, Al-Shaikh G. Recurrent urinary tract infections management in women: a review. Sultan Qaboos Univ Med 2013; 13: 359-67.
11. Guglietta A. Recurrent urinary tract infections in women: risk factors, etiology, pathogenesis and prophylaxis. Future Microbiol 2017; 12: 239-46.
12. Winblad U, Simpson-Hebert M. Ecological Sanitation - Revised and enlarged edition 2004; 67
13. Malik RD, Wu YR, Zimmern PE. Definition of recurrent urinary tract infections in women: which one to adopt? Female Pelvic Med Reconstr Surg 2018; 24: 424-9.
14. Concia E, Bragantini D, Mazzaferri F. Clinical evaluation of guidelines and therapeutic approaches in multi drug-resistant urinary tract infections. J Chemother 2017; 29: 19-28.
15. Zowawi HM, Harris PN, Roberts MJ, et al. The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nat Rev Urol 2015; 12: 570-84.
16. Bonkat G. Bartoletti RF. Bruyère F, et al. Wullt Guidelines Associates: EAU Guidelines on Urological Infections 2017; 14.
17. Raz R, Gennesin Y, Wasser J, Stoler Z, Rosenfeld S, Rottensterich E, Stamm WE. Recurrent urinary tract infections in postmenopausal women. Clin Infect Dis 2000; 30: 152-6.
18. Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med 1993; 329: 753-6.
19. Naber KG, Cho YH, Matsumoto T, Schaeffer AJ. Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. Int J Antimicrob Agents 2009; 33: 111-9.
20. Wagenlehner FM, Vahlensieck W, Bauer HW, et al. Prevention of recurrent urinary tract infections. Minerva Urol Nefrol 2013; 65: 9-20.
21. Sarikaya K, Senocak C, Ibis MA, Sadioglu FE, Ciftci M, Bozkurt OF. The effect of bladder pain syndrome/interstitial cystitis on partner sexual functions. J Ist Faculty Med 2022; 85: 110-6.

Original Article

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Acute cholecystitis during the COVID-19 pandemic: is percutaneous cholecystostomy a good alternative for treatment?

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ABSTRACT

Aim: To evaluate the efficacy, safety, and results of percutaneous cholecystostomy in patients with acute cholecystitis diagnosed with COVID-19.

Material and Method: The demographic characteristics, comorbidities, and acute cholecystitis grading of patients according to the Tokyo guideline 2018 (TG18) were evaluated. Mortality, laboratory parameters, radiological findings, physical status scores according to the American Society of Anesthesiologists (ASA) assessment, and the Charlson Comorbidity Index (CCI) were retrospectively evaluated in a total of 38 patients who underwent percutaneous cholecystostomy.

Results: The mean age of the 38 patients was 75±9 years, and 21 (55.3%) were female and 17 (44.7%) were male. According to TG18, 33 (86.8%) of the patients had grade II and five (13.2%) had grade III cholecystitis, while there was no grade I case. The mean CCI of the patients was 7.32±2.1. The ASA scores were mostly IIIE, followed by IIE. The COVID-19 test was positive in 33 (86.8%) of the patients. Mortality developed in four (10.5%) patients during hospitalization.

Conclusion: Percutaneous cholecystostomy can be considered as a safe, effective, and alternative method in the treatment of patients with acute cholecystitis.

Keywords: Acute cholecystitis, COVID-19, percutaneous cholecystostomy

INTRODUCTION

Acute cholecystitis (AC) is an emergency that mostly occurs as a result of gallbladder infection. It usually presents with pain in the right upper abdomen and under the right scapula, nausea, vomiting, and occasionally fever. According to the World Society of Emergency Surgery and Tokyo Guidelines, early laparoscopic surgery is the gold standard recommended to be performed as soon as the diagnosis has been made and the risk of choledocholithiasis has been evaluated (1,2). While conservative treatment is indicated in patients with a high risk of morbidity or mortality, percutaneous cholecystostomy (PC) is recommended as an alternative treatment method if the patient does not respond to conservative treatment (2).

During the COVID-19 pandemic, medical organizations such as the Society of American Gastrointestinal and Endoscopic Surgeons and the European Association for Endoscopic Surgery have suggested that an alternative approach to surgery, i.e., antibiotic therapy, PC, and watch-wait, should be preferred in as cases where possible (3). The onset of the pandemic was difficult in many aspects. Most importantly, there was no safe environment in the hospital for patients or healthcare workers. Furthermore, treatment guidelines for the management of acute surgical disease in patients with COVID-19 were initially inadequate.

In Turkey, the first case of COVID-19 was officially reported on March 11, 2020. There are studies in the literature in which laparoscopic surgery and endoscopic procedures are not recommended in case of suspected or diagnosed COVID-19 disease (4).

Studies have reported that the diagnosis or suspicion of COVID-19, as well as low reserve and high comorbidity

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may increase the risk of perioperative morbidity and mortality (4). In the current study, the efficacy, safety, and results of PC were evaluated in patients with AC diagnosed with COVID-19.

MATERIAL AND METHOD

The study was initiated with the approval by the Ankara City Hospital Clinical Researches Ethics Committee (Date: 03.08.2022, Decision No: E2-22-2240). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

Patient Data

The records of patients admitted to the General Surgery/ Emergency Surgery Service of Ankara City Hospital and underwent PC between September 2020 and May 2022 were retrospectively screened from the hospital's electronic system. From these records, demographic characteristics, comorbidities, and AC grading criteria according to the Tokyo guideline 2018 (TG18) were obtained. Mortality, laboratory parameters, radiological findings, physical condition scores according to the American Society of Anesthesiologists (ASA) assessment and the Charlson Comorbidity Index (CCI) were evaluated. Patients with coagulopathies or perforated gallbladder and those without gallstones were not included in the study. As a result of the eligibility evaluation, 38 patients were included in the study. The diagnosis of AC was confirmed using TG18 based on clinical, laboratory, and radiological findings. All grade I, II, and III acute cases according to TG18 were included in the study. In all the patients, oral nutrition was discontinued, and intravenous hydration and medical therapy with antibiotics (second-generation cephalosporin) were started.

PC was performed by a radiologist using the ultrasound-guided Seldinger technique and placing an 8-12-F catheter into the gallbladder through the transhepatic route. During the intervention, first, aspiration was performed, and then the gallbladder and bile ducts were visualized. After the catheter was inserted, the position of the catheter was confirmed using a contrast agent. The patency of the cystic duct and distal common bile duct was evaluated using a cholecystogram. The decision to remove the catheter was made according to the contrast transition and clinical improvement in the cystic duct and distal common duct.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, United States) version 16.0 for Windows were used for statistical analysis of the data. In addition to descriptive statistical methods (mean and standard deviation), the distribution of data was expressed as a percentage.

RESULTS

The age of the 38 patients included in the study was 75±9 years, and 21 (55.3%) were female and 17 (44.7%) were male. According to TG18, 33 (86.8%) of the patients had grade II and 5 (13.2%) had grade III AC, while there was no grade I case. The mean CCI of the patients was 7.32±2.1. The ASA scores of the patients were mostly IIIE, followed by IIE. The COVID-19 test was positive in 5 (13.2 %) of the patients. The remaining patients tested negative.

Mortality developed in four (10.5%) patients during hospitalization. Catheter removal was performed on average 21 (14-42) days after catheterization according to the clinical and laboratory data of the patients. Elective cholecystectomy was performed in four (10.5%) patients, of whom all were negative for COVID-19. The demographic and clinical data of all the patients are summarized in **Table 1**. Among the comorbidities of the patients, hypertension was the most common (n=29, 76.3%), followed by cerebrovascular and nephrological diseases. No catheter-related complications were observed in patients after PC; however, acute pancreatitis, hepatic abscess, AC recurrence, and cerebrovascular disease developed due to other causes. **Table 2** and **Table 3** summarize the comorbidities of the patients and complications that occurred after PC, respectively.

Table 1. Demographic data and clinicopathological characteristics of the patients

Variables	Number of patients (n=38) (%)
Age (mean±SD)	75±9
Gender	
Female	21 (55.3)
Male	17 (44.7)
Tokyo Guideline 2018 grade (%)	
Grade I	0
Grade II	33 (86.8)
Grade III	5 (13.2)
CCI (mean±SD)	7.32±2.1
ASA score	
IE	0
IIE	16 (42.1)
IIIE	20 (52.6)
IVE	2 (5.3)
COVID-19 positivity	
(-)	33 (86.8)
(+)	5 (13.2)
Cholecystectomy	4 (10.5)
Mortality	4 (10.5)
Catheter Removal Time (days, mean, min-max)	21 (14-42)

SD: Standard Deviation, ASA: American Society of Anesthesiology, CCI: Charlson Comorbidity Index

Table 2. Comorbidities of the patients

Comorbidity	Patient number (n=38) (%)
Hypertension	29 (76.3)
Diabetes mellitus	6 (15.8)
Chronic renal failure	10 (26.3)
Neurological disease	18 (47.4)
History of cerebrovascular disease	13 (34.2)
Congestive heart failure	13 (34.2)
Coronary artery disease	5 (13.2)
Chronic obstructive pulmonary disease	5 (13.2)
History of malignancy	2 (5.3)

Table 3. Complications that developed after percutaneous cholecystostomy

Complication	Patient number (n=38) (%)
Cholecystostomy-related	-
Other	4 (10.4)
Acute biliary pancreatitis	1 (2.6)
Hepatic abscess	1 (2.6)
Recurrence of acute cholecystitis at week 3	1 (2.6)
Cerebrovascular event	1 (2.6)

DISCUSSION

PC is one of the alternative treatment methods to conservative or surgical intervention in cholecystitis. PC has become a procedure preferred in patients with high comorbidity, advanced age, and generally poor conditions that make them unsuitable for surgery. Furthermore, the COVID-19 pandemic has resulted in an increase in the number of PCs performed. In particular, the risk of viral transmission due to surgical smoke and uncertainties concerning the evacuation of carbon dioxide gas after laparoscopic procedures have led to an increased tendency toward non-surgical treatments (5).

A typical radiological finding in patients with COVID-19 is the appearance of ground glass opacity in the form of a nodule or mass located in the peripheral and posterior position, usually in the form of organized pneumonia. In addition, consolidations, and linear, curvilinear, and perilobular opacities may also be present (6,7). In these patients, pulmonary involvement, additional comorbidities, and the presence of AC increase the morbidity and mortality associated with the surgical procedure. In a study conducted in Wuhan, China, it was determined that 41% of patients hospitalized with COVID-19 developed acute respiratory distress syndrome (ARDS), and an age over 65 years, diabetes mellitus, and hypertension were factors associated with ARDS development (8). The coexistence of AC and COVID-19 is rarely seen. In such cases, care should be taken in terms of treatment selection and planning. Laparoscopic cholecystectomy is currently the most accepted treatment option in the treatment of AC (9); however, this operation is performed by creating an artificial pneumoperitoneum, and ultrasonic or electrical equipment used generates large volumes of surgical fumes, placing the surgical team at risk of aerosol exposure. Therefore, laparoscopic surgery and endoscopic procedures are generally not recommended in patients with diagnosed or suspected COVID-19 (10). Initial data from China indicated that asymptomatic COVID-19-positive patients undergoing early surgery who developed pneumonia had an increasing global mortality rate and adverse clinical outcomes (11). For this reason, most elective operations, especially those requiring intensive care support, were postponed (12). PC is a good alternative method in these difficult-to-manage cases. In the current study, the coexistence of COVID-19 with AC was detected in 13.2% of the patients. PC was preferred as priority treatment in the majority of cases due to the presence of comorbidities.

A CCI above 6 is a factor associated with increased postoperative complications, and there is a strong correlation between the ASA grade and the decision for radiological and potential surgical treatment (13). In our study, the mean CCI of the patients was 7.32±2.1, and the ASA score was mostly IIE and above.

PC should be kept in mind as an alternative treatment method in case of abscess and sepsis in AC. Today, local symptoms and inflammatory response can be controlled with PC (14). Clinical success is generally defined as a decrease in fever, leukocyte count, and pain within 72 hours (15). In a review by Winbladh et al. (15), it was reported that in up to 40% of patients undergoing PC, the procedure was performed electively. However, in the current study, only four (10.5%) patients underwent elective cholecystectomy. This lower rate compared to the literature may be associated with the majority of our patients having had COVID-19.

The pandemic has had a great impact on the approach to many surgical emergencies, including the alteration of surgical priorities in the treatment of AC. Several studies have reported a trend toward more conservative approaches, such as the use of antibiotics or PC for the treatment of AC compared with early laparoscopic cholecystectomy, which was widely used in the pre-pandemic period.

The important limitations of this study are its retrospective nature and small patient population.

CONCLUSION

PC can be considered as a first-line treatment option, as well as being an alternative and safe method in high-risk patients, including those with comorbidities and COVID-19. In addition, PC is a good bridging treatment option in cases planned to undergo elective cholecystectomy.

There is no person/organization that supports the study financially and the authors do not have any interest-based relationship.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval by the Ankara City Hospital Clinical Researches Ethics Committee (Date: 03.08.2022, Decision No: E2-22-2240).

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

Referee Evaluation Process: Externally peer-reviewed.

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

REFERENCES

1. Ansaloni L, Pisano M, Coccolini F, et al. 2016 WSES guidelines on acute calculous cholecystitis. World J Emerg Surg 2016; 11: 1-23.
2. Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). Journal of Hepato-biliary-pancreatic Sci 2018; 25: 41-54.
3. Stavridis K, Liosis I, Konstantinidis MK, Kondylis G, Ioannidis A. COVID-19 and Acute Cholecystitis Management: A Systematic Review of Current Literature. Front Surg 2022; 9: 871685.
4. Karaca AS, Özmen MM, Uçar AD, Yastı AÇ, Demirer S. COVID-19'lu hastalarda genel cerrahi ameliyathane uygulamaları. Turk J Surg 2020; 36: 6-10.
5. Antunes D, Lami M, Chukwudi A, et al. COVID-19 infection risk by open and laparoscopic surgical smoke: a systematic review of the literature. The Surgeon 2021; 19: e452-e61.
6. Rotzinger D, Beigelman-Aubry C, Von Garnier C, Qanadli S. Pulmonary embolism in patients with COVID-19: time to change the paradigm of computed tomography. Thromb Res 2020; 190: 58-9.
7. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020: 200642.
8. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Int Med 2020; 180: 934-43.
9. Loozen CS, van Santvoort HC, van Duijvendijk P, et al. Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute cholecystitis in high risk patients (CHOCOLATE): multicentre randomised clinical trial. BMJ 2018; 363: k3965.
10. COVID, ACS. 19: elective case triage guidelines for surgical care. ACS website Published March. 2020: 24.
11. Ding BTK, Tan KG, Oh JY-L, Lee KT. Orthopaedic surgery after COVID-19–a blueprint for resuming elective surgery after a pandemic. Int J Surg 2020; 80: 162-7.
12. Zheng MH, Boni L, Fingerhut A. Minimally invasive surgery and the novel coronavirus outbreak: lessons learned in China and Italy. Ann Surg 2020; 272: e5-e6.
13. Shakir T, Matwala K, Vasan A, Karamanakos S. Percutaneous cholecystostomy for acute cholecystitis: a three-year single-centre experience including during COVID-19. Cureus 2021; 13: 12.
14. Griniatsos J, Petrou A, Pappas P, et al. Percutaneous cholecystostomy without interval cholecystectomy as definitive treatment of acute cholecystitis in elderly and critically ill patients. Southern Med J 2008; 101: 586-90.
15. Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB 2009; 11: 183-93.

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The impact of FVC/DLCO ratio on diagnosis of pulmonary hypertension and disease prognosis in idiopathic pulmonary fibrosis

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ABSTRACT

Introduction: Idiopathic pulmonary fibrosis is a chronic progressive fibrotic lung disease of unknown etiology that occurs most commonly in older adults. The presence of pulmonary hypertension in Idiopathic pulmonary fibrosis is associated with poor prognosis and mortality. Literature suggests that the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio has a positive predictive value for the diagnosis of pulmonary hypertension. Therefore, this study aimed to investigate the impact of forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio on the diagnosis of pulmonary hypertension and disease prognosis in Idiopathic pulmonary fibrosis patients.

MATERIAL AND METHOD: Forty-eight patients diagnosed with Idiopathic pulmonary fibrosis were included in the study. Patient records, echocardiographic and spirometric data were retrospectively reviewed.

Results: The average pulmonary arterial pressure was observed to be 32.8 (±9) mmHg, with the second-year follow-up pulmonary arterial pressure at 40.8 (±17.2) mmHg and the fourth-year follow-up pulmonary arterial pressure at 51 (±23.6) mmHg. In those diagnosed as pulmonary hypertension, the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio was initially 1.54 (±0.72). By the second year, it was 1.61 (±0.45), and by the fourth year, it was 1.87 (±0.8). It was found that the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio tended to increase when pulmonary artery pressure increased during the follow-up period.

Conclusion: We found that low six- minute walking test distance was an important marker for the diagnosis of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and that the presence of desaturation was also significantly associated with survival in pulmonary hypertension. Although we did not find it statistically significant, we found that both pulmonary arterial pressure and the the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio increased with progressive disease duration after diagnosis in patients with IPF. We believe that the the forced vital capacity to diffusion capacity of the lung for carbon monoxide ratio is an important marker for early detection of pulmonary hypertension and prognosis in idiopathic pulmonary fibrosis.

Keywords: Idiopathic pulmonary fibrosis, pulmonary hypertension, diffusion capacity

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic lung disease of unknown etiology that commonly occurs in older adults and is characterized by a histopathologically or radiologically typical interstitial pneumonia pattern (1). In IPF, symptoms develop over time and are usually associated with exertional dyspnea and dry cough. Progressive dyspnea is an important symptom that indicates disease progression and mortality (2).

Pulmonary function tests are essential for monitoring the clinical course of IPF. Forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) are considered the most critical parameters of pulmonary function tests (PFT) in IPF patients (3). The rate of decline of FVC has been used as a marker of disease progression because it is associated with mortality (4). Diffusion capacity of the lung for carbon monoxide measures another physiological deficiency (gas diffusion) associated with pulmonary fibrosis. It has also been reported to be associated with pulmonary hypertension

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(PH), considered a crucial concomitant disease of IPF. Forced vital capacity and DLCO may not be equally affected in pulmonary fibrosis, and pulmonary function test results may be normal in some IPF patients (3).

The presence of comorbidities in IPF patients may affect survival and quality of life and lead to disease progression. Some comorbidities, such as PH, may also be a consequence of IPF itself (5). The presence of PH in IPF is significantly associated with poor prognosis and mortality. In particular, concomitant pulmonary vascular disease in patients with advanced pulmonary parenchymal disease results in worse outcomes than a diagnosis of IPF alone (6). The overall prevalence of PH in IPF has been reported to be 36-86% and is attributed to hypoxemic vasoconstriction and destruction due to progressive fibrosis of the vascular bed (7). Presyncope or syncope, dyspnea not consistent with radiology and PFT, severely reduced diffusion capacity (DLCO < 30% predictive value), short walking distance, oxygen saturation below 85%, worsening heart rate during 6-minute walking test (6-MWT), also elevated BNP, pulmonary artery diameter/aortic diameter > 1 on thorax computed tomography (CT), increased right ventricular systolic pressure on echocardiography, enlargement of right heart chambers, and right ventricular dysfunction strongly suggest PH in a patient with IPF. However, the relationship between pulmonary artery pressure (PAP) and respiratory functions and the extent of fibrosis has not been demonstrated radiologically. Studies have shown that specific treatment is not effective in PH due to IPF and, in some cases, even leads to clinical worsening. Therefore, specific drug therapy has no place in PH due to IPF. However, it is recommended that patients with FVC greater than 70% and mean PAP > 35 mmHg measured by central cardiac catheterization should be referred to pulmonary artery hypertension (PAH) centers for treatment (8-11).

In the literature, the ratio of FVC to DLCO (FCV/DLCO) > 1.5 in patients with systemic sclerosis has been interpreted as an indicator of PH. In addition, the FVC/DLCO ratio has been shown to have a positive predictive value of 71% and a negative predictive value of 81% in determining PH development (12). Moreover, it has been shown in the literature that DLCO% < 55% and FVC/DLCO ratio > 1.4 may indicate the presence of PH (13,14). In view of this information, the aim of this study is to investigate whether FVC/DLCO ratio can be used to diagnose PH in IPF patients and what impact it has on prognosis.

MATERIAL AND METHOD

The study was carried out with the permission of Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.06.2022, Decision No: 2012-KAEK-15/2538). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was not obtained from the patients due to retrospective design.

The medical records of 72 patients who were followed up with the diagnosis of radiological and/or pathological IPF in our hospital's 8th Chest Diseases Polyclinic between January 2014 and June 2017 were retrospectively reviewed. Patients who did not have PFTs and echocardiographic examination at baseline, who were not followed up in the following 4 years, and who had comorbidities that could lead to an increase in PAP, such as heart failure, COPD, and collagen tissue disease, were excluded from the study. Thus, 48 patients could be enrolled in the study.

Data Collection

Gender, age, comorbidities, diagnosis dates, 6-MWT results at diagnosis, spirometric tests (FVC%, FEV1%, FEV1%/FVC% ratio, DLCO) and the pulmonary parenchymal findings on thorax CT at diagnosis, transthoracic echocardiography data at baseline and at the following 2 and 4 years, were retrospectively obtained from the hospital medical records system and patient files. Data were analyzed and recorded by the same researchers.

The presence of PH was determined by noninvasive transthoracic echocardiography. Transthoracic echocardiographic analysis was performed using a Philips HD 11 XE ultrasound machine with an S5-1 transducer (Koninklijke Philips N.V., Amsterdam, The Netherlands). Echocardiographic examination was done in the left lateral decubitus position. Evaluation of PAP was made by calculating the systolic transtricuspid gradient (by Bernoulli's equation using the maximum tricuspid regurgitation velocity measured by continuous wave Doppler) and adding an assumed right atrial pressure (15). A systolic PAP above 30 mmHg on echocardiography was accepted as the presence of PH.

Spirometry was performed to determine FVC, forced expiratory volume in one second (FEV1), and FEV1/FVC with a spirometer (AS-507, Minato Medical Science, Tokyo, Japan) in accordance with the American Thoracic Society-European Respiratory Society guidelines (ATS-ERS) (16). The FVC and DLCO values obtained during the spirometric tests were calculated, and their relationship with the presence of PH was investigated. The distance traveled in a straight corridor during the 6-MWT was recorded according to ATS guidelines (17). By assigning points for each variable (gender, age, FVC, DLCO) in the GAP index and staging system, a total score between 0 and 8 was obtained (18).

Statistical Analysis

Subgroups were formed for binominal regression analysis, with age cutoff at 65 years, six-minute walking test at 370 meters, and desaturation defined as saturation on room air of 88% or less. For the overall evaluation of gender, age, and lung function, the GAP index was used as an additional parameter by removing the above parameters after the initial analysis for confirmation. To evaluate the distribution of the parameters, the Kolmogorov-Smirnov test was performed. Accordingly, Pearson or Kendall's tau was used for correlation analysis. A comparison of parameters and their role in predicting PH was made by regression analysis. A p-value of less than 0.05 was accepted as statistically significant. If present, any parameter with a proportion of missing data greater than 10% of total participants should be removed from the study. The statistical analysis program used was International Business Machines (IBM) Statistical Product and Service Solutions (SPSS) Edition 23.

RESULTS

A total of 48 patients were eligible for the study. All patients were on antifibrotic treatment. The mean age of the group was 65.9 (±7.01) years, and 6.2% (n=3) of the patients were female. Most patients were diagnosed by radiological examination (81.3%, n=39), and the GAP index staging of patients was in favor of stage 1 (45%, n=22). Family history was not present in most patients (95.8%, n=46). The mean package/year smoking was 27.6 (19.6), with 68.8% (n=33) of patients being ex-smokers, 14.6% (n=7) active smokers, and the remaining 16.7% (n=8) nonsmokers. Desaturation was absent in the majority of patients, with 16 (33.3%) patients classified as moderate and severe for severity of desaturation, and the mean pulse oximeter saturation score without supplemental oxygen support was 92% (±6) (**Table 1**).

Mean pulmonary artery pressure was 32.8 (±9) mmHg and increased to 40.8 (±17.2) during the follow-up period and to 51 (±23.6) at the last examination. A greater decrease in DLCO was observed in patients diagnosed with PH than in patients without PH, with the difference increasing during the follow-up period. At baseline, patients with PH had a mean DLCO of 43.8% (±15.3), compared with 59.4 (±18.5) in patients without PH, which increased from 40.4% (±16.5) to 76.1% (±17.3) at the final examination. The FVC/DLCO ratio showed a similar pattern: in those diagnosed with PH, the ratio was first 1.54 (±0.72), then 1.61 (±0.45), and finally 1.87 (±0.8), compared with 1.28 (±0.43), 1.19 (±0.43), and 1.07 (±0.09), respectively, in patients without PH during the follow-up period (**Table 2**).

Table 1. Demographic Data, Pulmonary Fibrosis Status and History

Age (Years,SD)	65.9 (7.01)
Sex (n, %)	
Male	45 (93.8)
Female	3 (6.2)
Diagnostic Method (n,%)	
Radiologic	39 (81.3)
Pathologic	9 (18.7%)
GAP Index Stage (n,%)	
Stage 1	22 (45)
Stage 2	13 (27.1)
Stage 3	13 (27.1)
Familial History (n,%)	
No	46 (95.8)
Yes	2 (4.2)
Smoking History (n,%)	
Nonsmoker	8 (16.7)
Active Smoker	7 (14.6)
Ex Smoker	33 (68.8)
Smoking Duration (Package*Year,SD)	27.6 (19.6)
Finger Clubbing (n,%)	
Absent	28 (58.3)
Present	20 (41.7)
Six Minute Walking Test (m, SD)	414 (120)
Saturation (%, SD)	92 (6)
Desaturation Severity (n, %)	
no	6 (12.5)
mild	26 (54.2)
moderate	6 (12.5)
severe	10 (20.8)

SD:Standart Deviation,GAP Index: Scoring system for pulmonary fibrosis severity.

Table 2. Echocardiography PAP, Pulmonary Hypertension and Pulmonanry Function Test Results During Diagnosis and Follow-up

	Diagnosis	1. Follow-up	2. Follow-up
PAP (mmHg,SD)	32.8 (9)	40.8 (17.2)	51 (23.6)
FVC (%,SD)	68.8 (16.5)	68.9 (16.5)	70.9 (18.4)
PHT Presence	62.5 (16.2)	60.2 (16.5)	63 (16.7)
No PHT	68.8 (15.8)	69.6 (12.3)	81.2 (17.6)
FEV (%,SD)	73 (17.0)	72.9 (17.0)	75.9 (17.2)
PHT Presence	64.2 (14.2)	64.1 (15.7)	69.3 (13.5)
No PHT	73.8 (16.8)	74.3 (14.7)	82.8 (19.6)
FVC/DLCO (SD)	1.32 (0.49)	1.37 (0.5)	1.5 (0.65)
PHT Presence	1.54 (0.72)	1.61 (0.45)	1.87 (0.8)
No PHT	1.28 (0.43)	1.19 (0.43)	1.07 (0.09)
DLCO (%,SD)	57.4 (18.4)	55.6 (19.2)	54.9 (21)
PHT Presence	43.8 (15.3)	39.3 (11.8)	40.4 (16.5)
No PHT	59.4 (18.5)	63.33 (18.8)	76.1 (17.3)

PAP: Pulmonary Artery Pressure. SD: Standart Deviation, PHT: Pulmonary Hypertension. FEV: Forced Expiratory Flow, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of Lung for Carbon Monoxide

Binominal logistic regression was performed to evaluate the influence of age, gender, performance parameters,

and FVC/DLCO ratio on the presence of PH during the follow-up period. The logistic regression model proved not to be statistically significant ($\chi2(4)=10.427$, p=0.108) and explained (Nagelkerke R2) 30.2% of the variance in PH. Of all parameters, only 6-MWT played a role in PH, with higher walking distance reducing the likelihood that PH occurred during follow-up. No correlation was found with the FVC/DLCO ratio (p=0.407) (**Table 3**).

Table 3. Logistic Regression AnalysisRegardingParameters on Pulmonary Hypertension

	B	SE	Wald	df	p
Gender	0.194	1.605	0.015	1	0.904
Age	0.031	0.055	0.313	1	0.576
Finger Clubbing	0.132	0.776	0.029	1	0.864
Six Minute Walking Test (m)	-0.011	0.005	4.831	1	0.028
Saturation (%)	0.071	0.106	0.444	1	0.505
FVC/DLCO	0.627	0.756	0.688	1	0.407
Constant	-5.694	10.487	0.295	1	0.587

Note: Gender is for females compared to males. Saturation result was taken from finger pulse oximeter at room air.

When evaluating the parameters in the regression analysis to predict PHT for survival, only saturation was found to be statistically correlated with survival in the Kendall-Tau correlation, with a saturation value of less than 88% in room air having a negative correlation with survival (correlation coefficient -0.434, p:0.003) (**Table 4**).

Table 4. Correlation between Parameters and Survival

Correlation to Survival	Correlation Coefficient	Sig. (2-tailed)	N
Age	0.014	0.923	48
Six Minutes Walking Test	-0.205	0.160	48
Desaturation	-0.434	0.003	48
FVC/DLCO	-0.213	0.163	44
PAB	0.049	0.735	48
Gender	-0.248	0.090	48

Note: Gender is for females compared to males. Saturation result was taken from finger pulse oximeter at room air and a result below 88% was accepted as desaturation. For age, patients were divided at 65 years old cut off. 370 meters were accepted as the SMWT cut-off. A ratio of FVC/DLCO at 0.88 was defined as the cut-off for the binomial analysis.

Area under the curve (AUC) analysis for the role of the FVC/DLCO ratio in classifying the presence of PH yielded a value of 0.624 and was not considered a highly predictive model (p:0.176). An FVC/DLCO ratio greater than 0.83 had a sensitivity and specificity of 93% and 96%, respectively, whereas a higher ratio of 1.2 had a sensitivity of only 50% and a specificity of 42% for predicting PH (**Figure 1**).

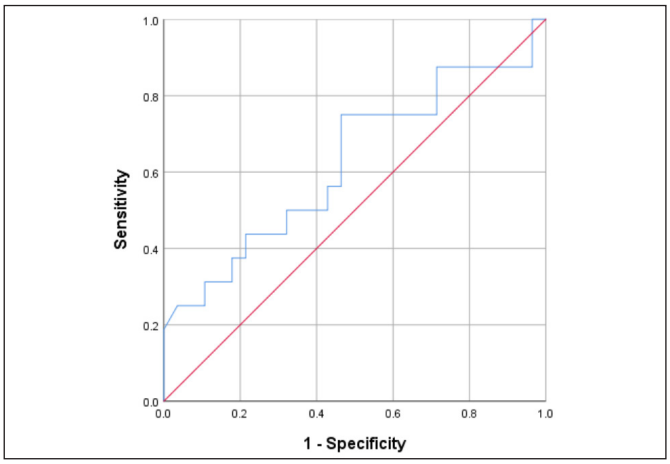

Figure 1. ROC Curve for FVC/DLCO and Pulmonary Hypertension Diagnosis During Follow-up.

DISCUSSION

The literature reports that the FCV/DLCO ratio is a useful marker for the diagnosis of PH (12,13). In our study, we investigated the usability of the FVC/DLCO ratio in IPF patients who also had PH. Consistent with the literatüre, we found that, DLCO was lower in patients with PH; and it was observed that DLCO tended to decrease as PAP increased during the follow-up. It was also observed that FVC/DLCO ratio was higher with the increase of PAP in the follow-ups; however, there was no statistical association between the presence of PH and this situation.

It has been reported that the prevalence of PH in IPF depends on the severity of IPF. In the early stages, PH affects <10% of patients. However, as IPF progresses, the prevalence of PH increases significantly (19). In the study by Teramachi et al. (18), the annual PAP change in patients with IPF was found to be 1.8 mmHg, and PAP was defined as an independent variable for mortality. Two other studies found that the frequency of PH on echocardiographic examination of patients with IPF ranged from 28 to 46% (9, 20). In our study, the frequency of PAP was lower at baseline, consistent with the literature, but increased with disease progression.

It is well known that restrictive ventilatory defects are common in IPF due to parenchymal fibrosis. Previous studies have reported that a decrease in FVC and DLCO predicts mortality in interstitial lung disease (21,22). Dyspnea, decreased DLCO, and rapid desaturation on exercise have been associated with the development of PH in IPF (20). In our study, the DLCO percentage was lower in patients with PH. It was observed that PAP tended to decrease, whereas PAP increased in periodic controls. In our study, DLCO percentage was lower in patients with PH; and it was observed that DLCO tended to decrease as PAP increased in periodic controls. In addition, we concluded that the DLCO and FVC value increased in

the patients without PH as the process progressed, while the FVC/DLCO ratio tended to decrease. Considering that all our patients received antifibrotic treatment, this result suggested that antifibrotic therapy is more effective in improving diffusion capacity in patients with IPF without PH.

In a multivariate linear analysis study, the FVC/DLCO ratio was shown to have a positive predictive value of 71% and a negative predictive value of 81% in determining the development of PH (12). Another study reported that DLCO < 55% and FVC/DLCO ratio > 1.4 were associated with PH (13). In our study, this ratio was also higher in patients with a higher PAP. It was also observed that this ratio was higher with the increase of PAP in the follow-ups; however, there was no statistical association between the presence of PH and this situation. Statistical significance could not be determined because of the small number of patients or the short follow-up period due to due to worse survival.

The study by Caminati et al. (23), showed that distance in 6-MWT was associated with mortality. A correlation between the 6-MWT and the values of PAP was also found in the literature. In addition, PH has recently been recognized as a possible complication of interstitial lung disease, particularly IPF (24,25). According to our results, lower 6-MWT distance and the presence of PH were statistically negatively correlated in patients with IPF.

Morbidity and mortality are high in IPF, and the clinical course varies widely among individuals (26). Low FVC and DLCO at baseline and a decrease in FVC or DLCO during the 6- or 12-month follow-up period predicted worse survival (27). In the study by Song et al. (28), 6-MWT distance, the presence of desaturation, and the presence of PH were associated with poor prognosis in IPF. Another study also pointed out that factors such as DLCO, presence of hypoxia, and PH had significant effects on survival (29). In our study, no significant association was found between FVC, DLCO, and 6-MWT distance and mortality. Only the presence of desaturation was associated with the survival.

This study has some limitations. First, the sample size was small. The study was retrospective. Because the included patients were those with mild-to-moderate IPF, their DLCO levels were slightly decreased, and their general condition and clinical features were mostly stable. Given the heterogeneity of IPF disease, our study group may represent only a fraction of the IPF population (especially those with preserved DLCO levels), and the result may not be valid for all patients with IPF. In addition, the fact that PAP is subjective may be limiting because it is evaluated by echocardiographic examination rather than right heart catheterization (RHC).

CONCLUSION

Because PH is a common complication of IPF and affects the clinical course of patients, it is essential to identify markers that may be useful for early diagnosis and treatment. We found that low 6-MWT distance is an important marker for the diagnosis of PH in patients with IPF, and the presence of desaturation is also significantly associated with survival in PH. Although we did not find it statistically significant, we found that PAP and the FVC/DLCO ratio increased with progressive disease duration after diagnosis in patients with IPF. We believe that the FVC/DLCO ratio is an important marker for early detection of PH and prognosis in IPF.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.06.2022, Decision No: 2012-KAEK-15/2538).

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

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-824.
2. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet J Rare Dis 2008; 3: 8.
3. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic intersti tial pneumonias. Proc Am Thorac Soc 2006; 3: 315–21.
4. Zappala CJ, Latsi PI, Nicholson AG, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fbrosis. Eur Respir J 2010; 35: 830–6.
5. Cano-Jiménez E, Hernández González F, Peloche GB. Comorbidities and complications in ıdiopathic pulmonary fibrosis. Med Sci 2018; 6: 71.
6. Collum SD, Amione-Guerra J, Cruz-Solbes AS, et al. Pulmonary hypertension associated with ıdiopathic pulmonary fibrosis: current and future perspectives. Can Respir J 2017; 2017: 1430350.
7. Sherner J, Collen J, King CS, Nathan SD. Pulmonary hypertension in idiopathic pulmonary fibrosis: epidemiology, diagnosis, and therapeutic implications. Curr Respir Care Rep 2012; 1: 233-42.

8. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J 2008; 31: 1357-67.
9. Shorr AF, Wainright JL, Cors CS, et al. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J 2007; 30: 715-21.
10. Kimura, Taniguchi H, Kondoh Y, et al. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. Respiration 2013; 85: 456-63.
11. Nathan SD, King CS. Treatment of pulmonary hypertension in idiopathic pulmonary fibrosis: shortfall in efficacy or trial design? Drug Des Devel Ther 2014; 8: 875-85.
12. Zisman DA, Ross DJ, Belperio JA, et al. Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 2007; 101: 2153-9.
13. Steen VD, Graham G, Conte C, Owens G, Medsger TA Jr. Isolated diffusing capacity reduction in systemic sclerosis. Arthritis Rheum 1992; 35: 765-70.
14. Öztürk A, Kayacan O. Rising stars of DPLD survival: FVC and exercise desaturation. Turk J Med Sci 2018; 48: 826-32.
15. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984; 70: 657–62.
16. European RS, American Thoracic Society. ATS/ ERS Statementon respiratory muscle testing. Am J Respir Crit Care Med 2002;166: 518-624.
17. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012; 156: 684–95.
18. Raghu G, Behr J, Brown KK, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan a parallel, randomized trial. Annals of Internal Medicine 2013; 158: 641-9.
19. Teramachi R, Taniguchi H, Kondoh Y, et al. Progression of mean pulmonary arterial pressure in idiopathic pulmonary fibrosis with mild to moderate restriction. Respirology 2017; 22: 986-90.
20. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 129: 746-52.
21. du Bois R, Albera C, Bradford W, et al. Predictors of mortality in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2009; 179: A1114.
22. Hanson D, Winterbauer RH, Kirtland SH, Wu R. Changes in pulmonary function test results after 1 year therapy as predictors of survival in patients with idiopathic pulmonary fibrosis. Chest 1995; 108: 305-10.
23. Caminati A, Bianchi A, Cassandro R, Mirenda MR, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. Respir Med 2009; 103: 117-23.
24. Shapiro S. Management of pulmonary hypertension resulting from interstitial lung disease. Curr Opin Pulm Med 2003; 9: 426-30.
25. Strange C, Highland KB. Pulmonary hypertension in interstitial lung disease. Curr Opin Pulm Med 2005; 11: 452-5.
26. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011; 183: 431-40.
27. Salisbury ML, Xia M, Zhou Y, et al. Idiopathic pulmonary fibrosis: gender-age-physiology ındex stage for predicting future lung function decline. Chest 2016; 149: 491-8.
28. Song H, Sun D, Ban C, et al. Independent clinical factors relevant to prognosis of patients with ıdiopathic pulmonary fibrosis. Med Sci Monit 2019; 25: 4193–201.
29. Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med 2007; 176: 277–84.

Original Article

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What is the role of YouTube™ as a source of information on trichotillomania?

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ABSTRACT

Objective: YouTube™ is a very popular video site worldwide and is increasingly being used to access health information. The content in these videos is often incomprehensible and worse, contains inaccurate and incomplete information. This article aims to evaluate the reliability and usefulness of information about TTM available to patients on YouTube™.

Material and Method: This study has a cross-sectional design. 51 videos were reviewed. Global quality score (GQS), modified DISCERN and trichotillomania Youtube score (TTMYS) were used for the quality analysis of the videos. Video duration(sec), time since upload (months), Number of views/comments/likes/dislikes were analyzed.

Results: The majority of the videos (31.4%) were uploaded by physicians, and the least by hospitals (3.9%). The mean GQS score was 2.06±1.363, the modified DISCERN score was

2.06±1.348, and the TTMYS score was 8.45±3.126. The GQS scores 1-2 (low quality), 3 (moderate quality), and 4-5 (high quality) were 68.6%, 11.8%, and 19.6%, respectively. The vast majority of videos were rated as low quality.

Conclusion: The TTM related video content rewieved was largely inadequate. Information about the disease and treatment options were insufficient. It is necessary to either take a primary role in uploading high-quality videos or establish supervisory mechanisms for the security and accuracy of information.

Keywords: Trichotillomania information, Youtube video, quality

INTRODUCTION

Trichotillomania (TTM) is an impulse control disorder characterized by recurrent hair or eyebrow plucking that causes hair loss. It is often a chronic disease and difficult to treat. Although large-scale epidemiological studies are not available, smaller studies estimate that TTM affects 1-3.5% of adolescents and adults. The largest prevalence study to date, involving 2534 students, determined a lifetime prevalence of 0.6% (1).

It was described by the French dermatologist François Henri Hallopeau in 1889 (2). It was first classified as an impulse control disorder in the DSM-3 in 1987 and recorded as a mental health disorder. DSM-4 diagnostic criteria for TTM have difficulties in diagnosis and treatment, so the classification was changed in DSM-5. In DSM-5, TTM is included in the obsessive-compulsive disorder (OCD), excoriation disorder, body dysmorphic disorder, hoarding disorder, and obsessive-compulsive and related disorders section (3). TTM is four times more common in women than men (1,4).

TTM is often accompanied by diseases such as anxiety disorder, depression, skin picking disorder, and addiction. Individuals diagnosed with TTM tend to avoid social environments because they are ashamed of their appearance and fear being judged by their environment. This causes them to spend more time on social media and the internet (5).

Today, many people use online systems to get information about health (6). YouTube™ (http://www.youtube.com) is the most used visual information source in the world after Google in this sense. Undoubtedly, the fact that Youtube is free and easily accessible has a great role in its popularity (7). However, the content in these videos is often incomprehensible and, worse, contains inaccurate and incomplete information (8).

It has become an important source of visual information for patients, medical students, and even residents (9). Since the Internet allows anyone to upload content and is not subject to any regulation, it may contain misleading or false information (8). The fact that patients often turn

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to platforms such as YouTube™ to get information about their problems may lead to misdirection of patients and deterioration of the physician-patient relationship. For this reason, the quality and security of information in online systems are very important (9, 10).

To investigate the effectiveness of YouTube videos in patient education, the content, and reliability of YouTube videos on topics as diverse as rheumatoid arthritis, heart surgery decision, COVID-19 Vaccination During Pregnancy were examined (11-13).

The importance of this research is the evaluation of videos on YouTube to develop correct attitudes about TTM and its treatment. To the best of our knowledge, there is no study in the literature evaluating the quality of YouTube videos as a source of information for TTM patients. This article aims to evaluate the reliability and usefulness of information about TTM available to patients on YouTube™.

MATERIAL AND METHOD

This study has a cross-sectional design. Ethics committee approval was not obtained as there was no human or animal participation in the study, and the videos were public. The study according to the World Medical Association Declaration of Helsinki, as no patient data or materials were used and all videos used for the study are available on a public social media website (YouTube).

Video Search On Youtube™

Videos were searched with the keywords "Trichotillomania" and "Hair Pulling Disorder" on https://www.youtube.com/ on October 21, 2021. The top 200 videos were listed by relevance (the default option on YouTube™). Only English videos were included. Videos with advertisements (4), duplicate videos (7), non-English videos (11), irrelevant videos (121), and videos without audio narration (6) were excluded (**Figure**).

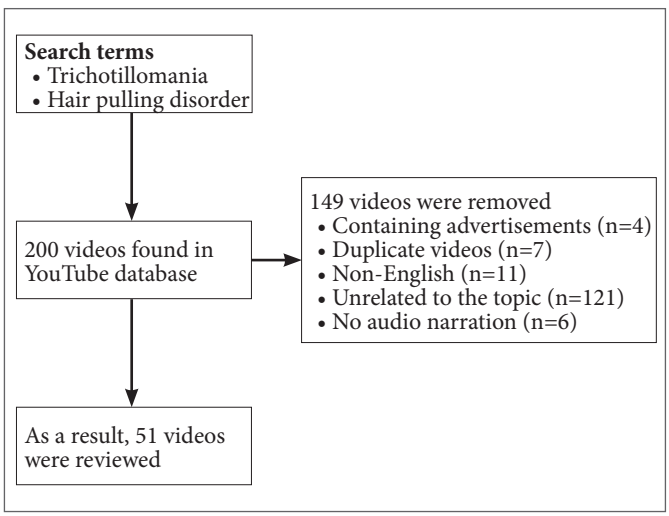

Figure. Working Flow

Video Features

Views, total video duration, total comments, total "likes" and "dislikes", time since upload date (months), video quality (pixels), and upload source were recorded. The upload source was categorized as physician, hospital, TV program, patient, psychologist, and independent user.

Video Quality Analysis

Video contents were evaluated by 2 independent mental health specialists (psychiatrists) (MA, PAA). A consensus was reached among the raters for the items that differed. Global Quality Score (GQS) and modified DISCERN were used for the quality analysis of the videos. GQS is a scoring system that evaluates the information level of the content using a 1 to 5 scoring system.

DISCERN was prepared by a group of experts from England to evaluate the appropriateness of treatment options in the texts. It evaluates the quality of the publication in 16 questions. The first 8 questions assess the credibility of the publication, the following questions examine specific details about treatment options, and the last question inquiries average quality. Each question is scaled from 1 to 5 points from No to Yes. If the answer is 'Absolutely Yes', 5 points are given; if 'Absolutely No', 1 point is given. The criteria evaluated in scoring are given in Table 2. A score of 63-75 is categorized as excellent, 51-62 as good, 39-50 as fair, 27-38 as poor, and 16-26 as very poor. The modified DISCERN score is calculated by dividing the obtained score by 16 and calculating the score per question. The score ranges from 0 to 5 points, with higher scores indicating greater reliability (14, 15).

There is no video scoring system for the evaluation of Trichotillomania videos. In this study, we evaluated all videos according to whether they contain information about diagnostic criteria (according to DSM-5), general treatment, medical treatment, therapies, alternative treatments, patient image, comorbidity, stressor, genetics, age, and differential diagnosis. Scoring was done by giving 1 point if it contains information and 0 points if it does not. The video that answered all questions received 12 points, and the video that did not answer any questions received 0 points. We named this scoring system TTM YouTube™ score (TTMYS).

Statistical Analysis

Statistical Package for the Social Sciences 22 (IBM, Armonk, NY, USA) was used for data analysis. The Shapiro-Wilk test was used to test the normality of the data. Mean, standard deviation, frequency, minimum, and maximum were used as descriptive statistics. The Kruskal-Wallis test was used to determine statistically significant differences of an independent variable between more than 2 groups. For pairwise comparisons, the Dunn- Bonferroni Post-Hoc method was used, followed by a Kruskal-Wallis test. Spearman test was performed for correlation analysis.

Inter-rater agreement was evaluated with the kappa coefficient. Results were considered significant at 95% confidence interval and P<0.05.

RESULTS

A total of 51 videos were analyzed. The features of the videos are given in **Table 1, Table 2 and Table 3**. The majority of the videos (31.4%) were uploaded by doctors, patients (23.5%), TV programs (17.6%), Independent (17.6%), Psychologists (5.9%), at least by hospitals (3.9%). According to the content analysis of the videos with TTM YouTube™ score (TTMYS), DSM-5 17.6%, general treatment 74.5%, medical treatment 33.3%, treatment 41.2%, alternative treatment 29.4%, using patient image 27.5%, talking about comorbidity 27.5%, talking about stressors 51.0%, genetic structure 7.8%, gender difference 21.6%, giving age information 25.5%, talking about differential diagnosis 25.5% rate was observed.

Table 1. Content analysis of videos

	n	%
DSM-5	9	17.6
General treatment	38	74.5
Medical treatment	17	33.3
Therapy	21	41.2
Alternative treatment	15	29.4
Using patient image	14	27.5
Talking about comorbidity	14	27.5
Talking about stressors	26	51.0
Genetic pattern	4	7.8
Gender difference	11	21.6
Giving age information	13	25.5
Talking about differential diagnosis	13	25.5

Table 2. Features of the videos

	Mean (Min - Max)
Video duration (sec)	797.76 (57-5229)
Time since upload (months)	38.37 (1-97)
Number of views	57160.51 (11-1145982)
Average number of views per month	2330.08 (1-71624)
Number of comments	185.31 (0-1400)
Number of likes	1240.69 (0-31000)
Number of dislikes	22.63 (0-259)
GQS score	2.06 (1-5)
DISCERN score	2.06 (1-5)
TTMYS score	8.45 (2-12)

Min: minimum, max: maximum, GQS: Global Quality Scale; TTMYS: Trichotillomania YouTube™ score

Data were not normally distributed. The mean GQS score was 2.06±1.363, the modified DISCERN score was 2.06±1.348, and the TTMYS score was 8.45±3.126. The GQS scores 1-2 (low quality), 3 (moderate quality), and 4-5 (high quality) were 68.6%, 11.8%, and 19.6%, respectively. The vast majority of videos were rated as low quality. According to GQS, 50% of high-quality videos came from TV programs. Again, according to the GQS system, 34% of the low-quality videos were those uploaded by patients. The Cohen kappa score was calculated as 0.883 for the GQS and 0.912 for the total DISCERN score. There was a significant correlation between DISCERN, GQS, and TTMYS scores. No correlation was detected in other parameters examined.

For GQS, post-hoc analysis determined a statistically significant difference between hospital-patient (hospital>patient p=0.02), hospital-independent (hospital>independent p=0.039), TV program-patient (TV program>patient p=0.005), and TV program-independent (TV program>independent p=0.022) groups.

For DISCERN, a statistically significant difference was observed between TV program-patient (TV program>patient p=0.003), and TV program-independent (TV program>independent p=0.028) groups.

For TTMYS, a statistically significant difference was observed between hospital- patient (hospital<patient p=0.037), TV program-patient (TV program patient p=0.013), and TV program-independent (TV program independent p=0.038) groups.

DISCUSSION

We found that most of the videos were uploaded by physicians. Unfortunately according to all three scoring systems, we found that the content and quality of the videos were insufficient.

YouTube™ includes studies in the field of psychiatry such as obsessive-compulsive disorder, generalized anxiety disorder, and Electroconvulsive therapy (ECT) (16-18). This study aims to evaluate the content and quality of YouTube™ videos as a source of information for TTM patients. To the best of our knowledge, there is no other study evaluating YouTube™ content as a patient

Table 3. Video quality ratings by the video source

Scoring systems	Physician (n=16)	Hospital (n=2)	Tv Program (n=9)	Patient (n=12)	Psychologist (n=3)	Independent (n=9)	p value
GQS	2.31 (1-5)	4.00 (4-4)	3.00 (1-5)	1.08 (1-2)	3.00 (1-5)	1.22(1-3)	0.001
DISCERN	2.31 (1-4)	3.50 (3-4)	3.11 (1-5)	1.08 (1-2)	2.67 (1-4)	1.33 (1-4)	0.001
TTMYS	7.81 (2-12)	4.00 (3-5)	6.33 (3-12)	10.50 (7-12)	7.33 (5-12)	10.33 (5-12)	0.001
Video duration	352.88 (87-1267)	232.50 (140-325)	2249.11 (94-5229)	710.58 (123-1810)	567.00 (57-1357)	456.11(69-1999)	0.001

Kruskal-Wallis test is presented as median (min-max). GAS: Global Quality Scale; Trichotillomania YouTube™ Score (TTMYS)

information source about TTM. Most of the videos share information about the treatment. Most of them were low-quality videos. A significant portion of the videos was uploaded by physicians, but the quality of these videos was also low. The TTMYS system demonstrated that the videos mostly talked about treatment and the presence of stressor factors. We think that it is very reasonable to talk about these two situations. Because the treatment part is an unknown, complex, and attraction-grabbing situation, while talking about well-defined stressors can also create the impression that the subject is known and dominated by the uploader.

GQS, DISCERN, and TTMYS systems showed a high correlation in video quality evaluation. According to the GQS scores, 68% of the videos were of low quality and had poor content. Previous studies evaluating YouTube™ content and quality as a source of information on various diseases have also found similar results (19). In a 2015 study by Macleod et al. (20), no video scored full marks from existing scoring systems. It was determined that more than half of the YouTube™ videos giving information about gallstones contained false information (21). In a study examining rheumatoid arthritis content, they found that about one- third of the videos contained misleading, false and unfounded information (11). The monthly average number of views per video was 2330.08±10028.161. In total, the videos we reviewed were watched 2,915,186 times. This shows how powerful YouTube™ is in data transfer.

Some studies have determined that videos with high-quality scores are longer videos (22, 23). Our findings are also compatible with the literature (p=0.001). The average duration of the videos we reviewed was 797.76±1173.545 seconds. However, when the video duration is too long, people may get bored, distracted, etc. Therefore, we think that this finding should be confirmed with larger samples. There is no study showing the ideal length of a good informational video. It is also possible for some videos to be extended, as those who make videos for YouTube™ can receive advertisements when they upload videos over 10 minutes. This emerges to be a confounding factor. Of all videos analyzed, 35.2% were longer than 10 minutes.

Our study was limited to analyzing only English-language videos on YouTube™. YouTube™ content changes from moment to moment over time. Besides, our study was limited to a direct YouTube™ search. We did not review videos on websites that contain health information other than YouTube™. Also, we examined the YouTube™ search engine with two limited titles (Trichotillomania and Hair Pulling Disorder). We did not take information about trichobezoar formation as a criterion in the contents. The videos were analyzed by two professional mental health professionals with knowledge of the literature on TTM, hence naturally biased physicians. It would have been more realistic to get the opinion of the public on this issue.

CONCLUSION

TTM patients are known to use YouTube™ to obtain information. There is no effective application to measure the quality and reliability of the information on YouTube™. Therefore, it is necessary to critically analyze the quality of YouTube™ videos. Physicians and academic institutions should be aware of the interest in this search for knowledge. It is necessary to either take a primary role in uploading high-quality, reliable videos or establish supervisory mechanisms for the security and accuracy of information.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study has a cross-sectional design. Ethics committee approval was not obtained as there was no human or animal participation in the study, and the videos were public. The study according to the World Medical Association Declaration of Helsinki, as no patient data or materials were used and all videos used for the study are available on a public social media website (YouTube).

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Grzesiak M, Reich A, Szepietowski JC, Hadryś T, Pacan P. Trichotillomania among young adults: prevalence and comorbidity. Acta loDermato-Venereogica 2017: 97.
2. Grant JE. Trichotillomania (hair pulling disorder). Indian J Psychiatry 2019; 61: S136.
3. Van Ameringen M, Patterson B, Simpson W. DSM-5 obsessive-compulsive and related disorders: clinical implications of new criteria. Depress Anxiety 2014; 31: 487-93.
4. Duke DC, Keeley ML, Geffken GR, Storch EA. Trichotillomania: a current review. Clin Psychol Rev 2010; 30: 181-93.
5. Vargiu AV, Magistrato A. Atomistic-level portrayal of drug–DNA interplay: a history of courtships and meetings revealed by molecular simulations. Chem Med Chem 2014; 9: 1966-81.
6. Velasco E, Agheneza T, Denecke K, Kirchner G, Eckmanns T. Social media and internet-based data in global systems for public health surveillance: a systematic review. Milbank Q 2014; 92: 7-33.

7. Madathil KC, Rivera-Rodriguez AJ, Greenstein JS, Gramopadhye AK. Healthcare information on YouTube: a systematic review. Health Informatics J 2015; 21: 173-94.
8. van Uden-Kraan CF, Drossaert CH, Taal E, et al. Health-related Internet use by patients with somatic diseases: frequency of use and characteristics of users. Inform Health Soc Care 2009; 34: 18-29.
9. Kumar N, Pandey A, Venkatraman A, Garg N. Are video sharing web sites a useful source of information on hypertension? J Am Soc Hypertens 2014; 8: 481-90.
10. Ketelaars PJ, Buskes M, Bosgraaf R, et al. The effect of video information on anxiety levels in women attending colposcopy: a randomized controlled trial. Acta Oncologica 2017; 56: 1728-33.
11. Singh AG, Singh S, Singh PP. YouTube for information on rheumatoid arthritis—a wakeup call? J Rheumatol 2012; 39: 899-903.
12. Arslan A. The role of YouTube® videos in heart surgery decision. J Health Sci Med 2021; 4: 372-6.
13. Doğru Ş, Akkuş F, Atci AA. Is youTube effective on COVID-19 vaccination during pregnancy. J Biotechnol Strategic Health Res 2022; 6: 51-7.
14. Charnock D. The DISCERN handbook. Quality criteria for consumer health information on treatment choices Radcliffe: University of Oxford and The British Library 1998: 7-51.
15. Som R, Gunawardana NP. Internet chemotherapy information is of good quality: assessment with the DISCERN tool. Br J Cancer 2012; 107: 403-4.
16. Nour MM, Nour MH, Tsatalou OM, Barrera A. Schizophrenia on YouTube. Psychiatr Serv 2017; 68: 70-4.
17. Abhishek P, Gogoi V, Borah L. Depiction of obsessive-compulsive disorder in YouTube videos. Inform Health Soc Care 2021; 46: 256-62.
18. Genc ES, Wu HE, Pinjari OF, et al. Image of electroconvulsive therapy in YouTube videos. J ECT 2020; 36: e19-e21.
19. Celik H, Polat O, Ozcan C, Camur S, Kilinc BE, Uzun M. Assessment of the quality and reliability of the information on rotator cuff repair on YouTube. Orthop Traumatol Surg Res 2020; 106: 31-4.
20. MacLeod MG, Hoppe DJ, Simunovic N, Bhandari M, Philippon MJ, Ayeni OR. YouTube as an information source for femoroacetabular impingement: a systematic review of video content. Arthroscopy 2015; 31: 136-42.
21. Lee JS, Seo HS, Hong TH. YouTube as a source of patient information on gallstone disease. World J Gastroenterol 2014; 20: 4066-70.
22. Gaş S, Zincir ÖÖ, Bozkurt AP. Are YouTube videos useful for patients interested in botulinum toxin for bruxism?. J Oral Maxillofac Surg 2019; 77: 1776-83.
23. Lena Y, Dindaroğlu F. Lingual orthodontic treatment: a YouTube™ video analysis. Angle Orthod 2018; 88: 208-14.

Original Article

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Which one is the most preferred anesthesia type in dental treatments of patients with special needs: sedation or general anesthesia?

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ABSTRACT

Aim: Patients with special needs, who have mental, physical or medical disabilities, were reported to have worse oral hygiene than their healthy peers. Disabled patients are usually uncooperated, and dental treatments of these patients are completed under several anesthesia types. Our aim was to compare anesthesia types in dental treatments of patients with special needs.

Material and Method: The study included review of uncooperated patients, who had physical or mental disabilities, between June 1, 2021 and June 1, 2022. Patients were divided into three groups due to their anesthesia types; sedation (Group S), laryngeal mask airway (LMA) (Group L), and nasotracheal intubation (Group N).

Results: In total 80 patients were analyzed; 4 patients excluded, 45 patients were in Group S, 19 patients were in Group L, and 12 patients were in Group N. Anesthesia times were significantly different between groups; 20 min in Group S, 25 min in Group L, and 45 min in Group N. Propofol use was significantly low ($p<0.001$) and ketamine use was significantly high in Group S ($p=0.002$). Number of tooth extractions was not significantly different between groups, but number of filling tooth was significantly high in Group N ($p=0.002$).

Conclusion: Sedation was the most preferred anesthesia type in dental treatment of patients with special needs. Although all three types of anesthesia can be used safely in dental treatments, we suggest that sedation can be considered as the first choice in tooth extraction in patients deemed appropriate by the anesthesiologist and dentist.

Keywords: Anesthesia, general anesthesia, dentistry, tooth, disabled persons

INTRODUCTION

Patients with special needs, who have mental, physical or medical disabilities, were reported to have worse oral hygiene than their healthy peers (1). Disabled patients are usually uncooperated, and dental treatments of uncooperated patients need to be completed under anesthesia (2). Dental anesthesia includes both sedation and general anesthesia. The decision to treat patients under sedation or general anesthesia has still further considerations, including the overall health of the patient, the preferences of the carers, the indicated procedures, operator/ facility-related factors or the cost (3). Even general anesthesia provides a relatively safe option for the dental treatment of patients, it is at higher risk of perioperative complications due to the presence of medical comorbidities. Unlike the healthy population, special needs patients are more likely to have medical comorbidities that can complicate the anesthesia (4-6). Therefore, preoperative assessments are essential to reduce risk of peri-operative and post-operative complications (7).

During the preoperative anesthesia assessment ASA Physical Status Classification System is often used. The literature has suggested that patients classifed as ASA III should be treated in hospital facilities (4). Even dental practitioners often prefer nasotracheal intubation for the dental treatment, anesthesiologists should be aware of any alterations in airway anatomy (5).

Guidelines for the pre-operative assessment of patients with special needs are also limited (3, 8-10). The British Society for Disability and Oral Health consensus (8) recommends that pre-operative assessments and consents should be conducted by both treating dental surgeon and anesthesiologist. In some cases, carers are not direct family members, and they may not be familiar with the patient's history. This can present difficulty to obtain suitable information regarding patient's

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history and previous anesthetic experience, in addition preoperative instructions like fasting or medication dosage, or postoperative instructions (11-13).

Ultimately, the purpose of dental anesthesia is to allow total oral rehabilitation, which consists of tooth extraction, tooth filling or tooth cleaning in a single session. Past studies of dental anesthesia in patients with special needs have resulted in conflicted results. The objective of this study was to compare anesthesia types in dental treatments of patients with special needs.

MATERIAL AND METHOD

The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 17.06.2022, Decision No: 46059562-020-566). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective study, we analyzed records of patients, who underwent dental treatment, including tooth extraction, tooth surface cleaning and tooth filling, under anesthesia between June 1, 2021 and June 1, 2022. All uncooperated ASA III patients with mental, physical or mental disability, and those who received dental treatment under anesthesia, were included in our study. Patients who were healthy or did not receive anesthesia for dental treatment were excluded. Peri-operative anesthetic management is standardized at our department. Anesthesiologist assessed the patient's general condition before the procedure.

According to anesthesiology department's protocol, intravenous (i.v.) cannula placement of patients was done at the floor, and patients came with an i.v. cannula to the preoperative area, where patients received a dose of 0.05 mg.kg-1 i.v. midazolam for premedication. In the operating room, electrocardiography, non-invasive blood pressure, and oxygen saturation were measured in every patient.

The decision of which anesthesia type would be used was determined by the anesthesiologist in consultation with the dentist. Anesthesiology department's protocol included nasal oxygen administration in all patients, who were planned to apply sedation during the treatment. Administered anesthetic agents were changed due to the anesthesiologist' preference including ketamine, propofol and fentanyl. The protocol suggested to monitore the sedation level with Ramsay Sedation Scale (RSS) and the procedure was not started before the patient had RSS of 5. If the procedure maintained with general anesthesia, which included laryngeal mask airway (LMA) and nasotracheal intubation, rocuronium (0,6 mg.kg-1) and sevoflurane (MAC=1) in a mixture of 50% oxygen and 50% air with 2 l.dk-1 flow rate were added to induction agents, which were ketamine, propofol and/or fentanyl as written in the protocol. Lungs were ventilated with a tidal volume of 6-8 ml.kg-1 and with a positive end-expiratory pressure of 5 cm H_2O. End-tidal carbon dioxide was maintained at between 35 and 40 mmHg by adjusting the respiratory rate.

Patient sex, age, weight, and disabilities were recorded as demographic variables. Peri-operative data included the anesthesia types, anesthesia time, anesthesia drugs, numbers of tooth extraction, tooth filling and tooth surface cleaning, and hospital length of stay (LOS). Patients were divided into three groups due to their anesthesia types: sedation (Group S), LMA (Group L), and nasotracheal intubation (Group N). The peri-operative data from three groups were analyzed. In post-operative data; patients' hospital length of stay was recorded.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked with kolmogorov-simirnov test. Kruskal-wallis test and mann-whitney U test were used for the comparison of quantitative data. Chi-Square test was used for the comparison of the comparison of qualitative data. SPSS 28.0 was used for statistical analyses.

RESULTS

The study included 80 patients, who underwent dental treatment with anesthesia between June 1, 2021 and June 1, 2022. Four patients were excluded due to the missing anesthesia records. Seventy-six patients were enrolled to the study (**Figure**). Demographic variables of patients were presented in Table 1. Of all 76 patients, the median age was 14 (8-23) years with 29 (38%) female patients, and the median weight was 45 (25-69) kilograms (kg). The most common disabilities were mental retardation (28%), cerebral palsy (26%), and epilepsy (24%). In peri-operative variables of all patients, the median anesthesia time was 25 (18-34) minutes, the median fentanyl dose was 0.2 (0-1) microgram/kg, the median propofol dose was 1.5 (0,6-2) mg/kg, and the median ketamine dose was 0 (0-1) mg/kg. Seventy (92%) patients had tooth extraction, 20 (26%) patients had tooth filling, and 10 (13%) patients had tooth surface cleaning.

Patients were divided into 3 groups according to their anesthesia types. Forty-five patients received (60%) sedation (Group S) and 31 (40%) patients received general anesthesia during dental treatments. Under general anesthesia there were 2 groups with 19 patients (25%), who received LMA (Group L), and 12 patients (15%), who received nasotracheal intubation (Group N). There was no significant difference in the demographic variables except cerebral palsy disability between the three groups (**Table**

1). Group L had significantly higher cerebral palsy patients than other groups. (p=0.035). In 2 group comparisons, Group L had significantly high cerebral palsy patients than Group S (p=0.044) and Group N (p=0.024). Anesthesia times were significantly different between groups. (p<0.001) Median anesthesia time was 20 (15-29) minutes in Group S, 25 (20-30) minutes in Group L, and 45 (3-54) minutes in Group N. In 2 group comparisons, Group N was significantly longer anesthesia time than Group S (p<0.001) and Group L (p=0.002).

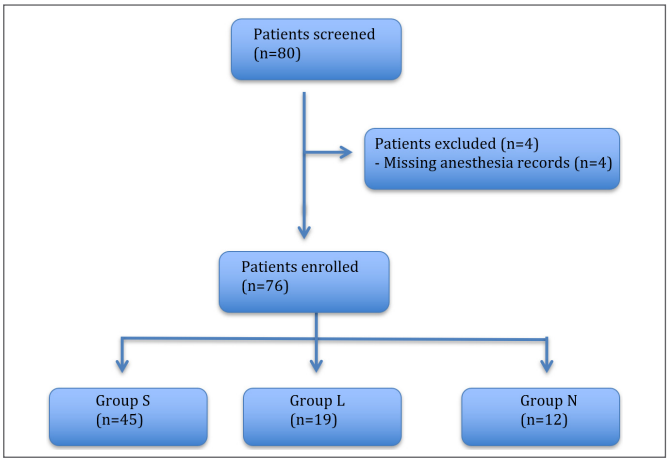

Figure. Flow chart

Propofol use was significantly low (p<0.001) and ketamine use was significantly high in Group S (p=0.002). In 2 group comparisons, Group S had significantly lower propofol use than Group L (p<0.001) and Group N (p<0.001); and significantly higher ketamine use than Group L (p=0.007) and Group N (p<0.006). In Group S (n=45); 12 patients did not receive propofol, 17 patients did not receive ketamine, and 23 patients did not receive fentanyl. In Group L (n=19); 1 patient did not receive propofol, 16 patients did not receive ketamine and 8 patients did not receive fentanyl. In Group N (n=12); 9 patients did not receive ketamine and 6 patients did not receive fentanyl.

Number of tooth filling patients and number of tooth were significantly high in Group N. (p=0.002) In 2 group comparisons, Group N had significantly higher tooth fillings patients than Group S (p=0.001) and Group L (p=0.011); and significantly higher tooth fillings than Group S (p=0.001) and Group L (p=0.017) (**Table 2**). There was no peri-operative adverse events including vomiting, pulmonary aspiration, laryngospasm or apnea in the current study. All patients were discharged from the hospital at the same day with procedure.

Table 1. Demograhic variables

Variables	Total (n=76)	Group S (n=45)	General Anesthesia		P value
			Group L (n=19)	Group N (n=12)	
Age, yr	14 (8-23)	13 (7-22)	11 (8-27)	18 (9-23)	0.525
Gender					0.066
Female	28 (37)	14 (31)	6 (32)	8 (66)	
Male	48 (63)	31 (69)	13 (68)	4 (34)	
Weight, kg	45 (25-69)	40 (21-57)	43 (27-70)	62 (34-80)	0.119
Disability					
Mental redardation	21 (27)	13 (29)	5 (26)	3 (25)	0.954
Cerebral palsy	20 (26)	10 (22)	9 (47)	1 (8)	0.035
Epilepsy	18 (23)	10 (22)	5 (26)	3 (25)	0.934
Autism	17 (22)	12 (27)	3 (26)	2 (17)	0.555
Down syndrome	14 (18)	8 (18)	3 (16)	3 (25)	0.800
Psychosis	2 (3)	1 (2)	0 (0)	1 (8)	1.000
Microcephaly	1 (1)	1 (2)	0 (0)	0 (0)	1.000

Data are presented as medians (interquartile ranges) or absolute numbers (percentages).

Table 2. Peri-operative variables of patients

Variables	Total (n=76)	Group S (n=45)	General Anesthesia		P value
			Group L (n=19)	Group I (n=12)	
Anesthesia time, min	25 (18.34)	20 (15-30)	25 (20-30)	45 (31-54)	<0.001
Anesthetic agents, mg/kg					
Propofol	1.5 (0.6-2)	1 (0-1.6)	2 (1.5-2.6)	2.1 (1.26-2.5)	<0.001
Fentanyl	0.2 (0-1)	0 (0-0.6)	0.5 (0-1.2)	0.35 (0-1)	0.359
Ketamine	0 (0-1)	0.7 (0-1.4)	0 (0-0)	0 (0-0.23)	0.002
Rocuronium	0 (0-0)	0 (0-0)	0 (0-0)	0.4 (0.23-0.5)	<0.001
Tooth extraction					
Number of patients	70 (92)	43 (96)	17 (90)	10 (83)	0.630
Number of tooth	4 (3-6)	4 (2-5)	5 (3-10)	3.5 (2-7)	0.111
Tooth filling					
Number of patients	20 (26)	8 (18)	4 (21)	8 (67)	0.002
Number of tooth	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-2.75)	0.002
Tooth cleaning					
Number of patients	10 (13)	3 (7)	3 (16)	4 (33)	0.759

Data are presented as medians (interquartile ranges) or absolute numbers (percentages).

DISCUSSION

The results of this study indicate that sedation was more preferred anesthesia type than general anesthesia in dental treatments of patients with special needs in daily practice. In our study 60% of patients underwent dental treatments with sedation. Our data are consisted with the literature, which suggested to consider general anesthesia only where other techniques have failed, due to the inherent risks, costs, and complications associated with treatment under general anesthesia (14-17). In addition, Infante et al. (18) emphasized the importance of ambulatory anesthesia with shortened waiting lists, patient satisfaction, and good quality of care. In our study LMA was more preferred than nasotracheal intubation with shorter anesthesia times. Similar to our results, Kim et al. (19) showed LMA had been preferred to use when short-term dental treatment was expected.

We showed no significant difference in the disabilities of patients between anesthesia types, except cerebral palsy. Cerebral palsy patients were mostly underwent dental treatments under general anesthesia. Our findings on the relationship between the disability and anesthesia type agree with those reported by Loyola-Rodriquez et al. (20), who assessed 38 cerebral palsy patients, and they mostly applied general anesthesia compared to sedation (57% vs. 24%). Unlike Hulland et al. (21), we observed no significant relationship between autism, epilepsy, and dental treatment under general anesthesia.

Our study showed that propofol was mostly preferred in general anesthesia than sedation. Moreover, ketamine was the most preferred agent in sedation with 0,7 mg/kg dosage. The reason for the preference of ketamine in sedation may be the reason that it does not cause respiratory depression. Our data differ from Loyola-Rodriquez et al. (20) study, which showed propofol preference for sedation. Likewise our patients distribution, Ouchi et al. (22) study had a population including epilepsy, autism, and cerebral palsy. Also, they showed higher propofol dosages, which was approximately 7 mg/kg, than our study, which we found 1,5 mg/kg in all patients.

Our other result was relevant to the anesthesia times. Even there was no significant difference in number of extracted tooth between groups, general anesthesia group, in particular Group N, had longer anesthesia times than sedation group (45 min vs. 20 min, $p<0.001$). Tooth extraction was a painful procedure, and patients with sedation did tolerate the procedure with shorter anesthesia times. Also, anesthesia times in our study were significantly shorter than other studies. Literature showed longer anesthesia times, which were 50 and 120 minutes, than our study (20,21). Keles et al. (23) compared nasotracheal intubation and LMA in pediatric patients, and likewise our study they found shorter anesthesia time in LMA group than nasotracheal intubation group.

In dental treatments, tooth extraction was the most applied treatment, which was performed in 92% of patients, and followed by tooth filling, which was performed in 26% of patients in the current study. There was not a significant difference between groups in extracted tooth numbers. Similar to our results, Keles et al. (23) found no significant difference in extracted tooth numbers between LMA and nasotracheal intubation group. In our study, tooth filling was mostly applied under general anesthesia. Contrary to Keles & Kocaturk study (23), we showed a significant difference between LMA and nasotracheal intubation in tooth filling. In addition, unlike Campbell et al. (24) study, which showed 95% of uncooperative pediatric patients underwent dental treatments under general anesthesia and the mean number of dental treatments were mostly consisted of 8 including crowns, fillings, and extractions, which we observed the mean number of extracted tooth number was 4.

Our study had several limitations. First, we did not record patients' daily medications, which can affect anesthesia agent doses. Second, we did not record the anesthesia emergence and post-operative care unit time.

CONCLUSION

Sedation was the most preferred anesthesia type in dental treatments of patients with special needs. Durations of sedation and general anesthesia in dental treatments were significantly different. Tooth filling treatment was mostly performed under general anesthesia. Although all three types of anesthesia can be safely used for dental treatments, we suggest that sedation can be considered as the first choice in tooth extraction in patients deemed appropriate by the anesthesiologist and dentist. As our cohort was limited with the dental anesthesia of patients with special needs, the results further suggest assessing sedation for dental treatments of patients. Additional studies are needed to confirm safety and applicability of sedation in dental treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Ethics Committee (Date: 17.06.2022, Decision No: 46059562-020-566).

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. Tesini DA. An annotated review of the literature of dental caries and periodontal disease in mentally retarded individuals. Spec Care Dentist 1981; 1: 75-87.
2. Roeters J, Burgersdijk R. The need for general anesthesia for the dental treatment of mentally handicapped patients: A follow-up study. ASDC J Dent Child 1985; 52: 344-6.
3. Prabhu NT, Nunn JH, Evans D, Girdler N. Development of a screening tool to assess the suitability of people with a disability for oral care under sedation or general anesthesia. Spec Care Dentist 2008; 28: 145-58.
4. Messieha Z. Risks of general anesthesia for the special needs dental patient. Spec Care Dentist 2009; 29: 21-5.
5. Wang YC, Lin IH, Huang CH, Fan SZ. Dental anesthesia for patients with special needs. Acta Anaesthesiol Taiwan 2012; 50: 122-5.
6. Jamjoom M, Al-Malik M, Holt R, El-Nassry A. Dental treatment under general anaesthesia at a hospital in Jeddah, Saudi Arabia. Int J Paediatr Dent 2001; 11: 110-6.
7. Lim MAWT, Borromeo GL. The use of general anesthesia to facilitate dental treatment in adult patients with special needs. J Dent Anesth Pain Med 2017; 17: 91-103.
8. British Society for Disability and Oral Health. The Provision of Oral Health Care under General Anaesthesia in Special Care Dentistry: A Professional Consensus Statement. British Society for Disability and Oral Health. 2009.
9. Intercollegiate Advisory Committee for Sedation in Dentistry. Standards for conscious sedation in the provision of dental care. 2015.
10. American Dental Association. Guidelines for the use of sedation and general anesthesia by dentists. Chicago, ADA House of Delegates. 2012.
11. Voytus ML. Evaluation, scheduling, and management of dental care under general anesthesia for special needs patients. Dent Clin North Am 2009; 53: 243-54.
12. Weaver JM. Special considerations concerning general anesthesia for dental treatment of handicapped patients. Anesth Prog 1995; 42: 93.
13. Garcia-Miguel F, Serrano-Aguilar P, Lopez-Bastida J. Preoperative assessment. Lancet 2003; 362: 1749-57.
14. Glassman P. A review of guidelines for sedation, anesthesia, and alternative interventions for people with special needs. Spec Care Dentist 2009; 29: 9-16.
15. Dougherty N. The dental patient with special needs: A review of indications for treatment under general anesthesia. Spec Care Dentist 2009; 29: 17-20.
16. Messieha Z, Ananda RC, Hoffman I, Hoffman W. Five year outcomes study of dental rehabilitation conducted under general anesthesia for special needs patients. Anesth Prog 2007; 54: 170-4.
17. Vargas Román Mdel P, Rodríguez Bermudo S, Machuca Portillo G. Dental treatment under general anesthesia: a useful procedure in the third millennium? Med Oral 2003; 8: 129-35.
18. Infante P, Gutierrez JL, Martín MJ, Hernández JM, García M. La cirugía oral y maxilofacial en pacientes especiales con discapacidad psíquica. Odonto- logía Práctica y Clínica 2000; 3:10-6.
19. Kim YJ, Hyun HK, Kim JW, et al. Clinical Usefulness of Proseal Laryngeal Mask Airway for Anesthesia during Dental Procedures in Children. J Clin Pediatr Dent 2015; 39: 179-82.
20. Loyola-Rodriguez JP, Aguilera-Morelos AA, Santos-Diaz MA, et al. Oral rehabilitation under dental general anesthesia, conscious sedation, and conventional techniques in patients affected by cerebral palsy. J Clin Pediatr Dent 2004; 28: 279-84.
21. Hulland S, Sigal MJ. Hospital-based dental care for persons with disabilities: a study of patient selection criteria. Spec Care Dentist 2000; 20: 131-8.
22. Ouchi K, Sugiyama K. Required propofol dose for anesthesia and time to emerge are affected by the use of antiepileptics: prospective cohort study. BMC Anesthesiol 2015; 15:34.
23. Keles S, Kocaturk O. Postoperative discomfort and emergence delirium in children undergoing dental rehabilitation under general anesthesia: comparison of nasal tracheal intubation and laryngeal mask airway. J Pain Res 2018; 11: 103-10.
24. Campbell RL, Shetty NS, Shetty KS, Pope HL, Campbell JR. Pediatric dental surgery under general anesthesia: uncooperative children. Anesth Prog 2018; 65: 225-30.

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The diagnostic value of complete blood parameters in determining the severity of community-acquired pneumonia in children

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ABSTRACT

Aim: In children, community-acquired pneumonia (CAP) has a high mortality and morbidity rate. Platelet, neutrophil, lymphocyte, monocyte, eosinophil, red cell distributions width (RDW), mean platelet volume (MPV), platelet distributions width (PDW), platelet to lymphocyte ratio (PLR), and neutrophil to lymphocyte ratio (NLR) have all been suggested as markers of systemic infection and inflammation. Several research, however, have centered on the clinical significance of blood parameters in pediatric CAP. We aim to determine the diagnostic value of complete blood parameters for CAP and to look into their relationship to disease severity.

Material and Method: A retrospective, the cross-sectional study enrolled children aged 3 months to 18 years who were diagnosed with CAP at Ankara Atatürk Sanatorium Training and Research Hospital's pediatrics clinics between January 2018 and June 2021, as well as age-matched healthy children. CAP case definition was made according to the CAP case definition defined by the World Health Organization (WHO). Patients were evaluated according to the criteria of WHO and British Thoracic Society 2011 guidelines as severe and mild CAP.

Results: 400 CAP and 400 control patients were included in the study. The mean age of the CAP group was 2.40±3.20 years and the control group was 2.38±3.17 years. Eosinophil, hemoglobin, MPV, PDW and PLR values of the CAP group was statistically significantly lower; leukocytes, lymphocyte, monocyte, neutrophil, basophil, platelet, RDW, and NLR levels of the CAP group were higher than the control group ($p<0.05$). 30.3% of the CAP patients had severe disease. The mean age of the severe group was 2.92±3.80 and 2.17±2.88 in the mild group. The ratio of males in the CAP group was 62%, while 80.2% in severe, 54.1% in the mild group ($p<0.001$).The mean hospitalization length for the severe group was 6.16±2.00 days and 4.89±1.78 days for the mild group ($p<0.001$). CRP, neutrophils, monocyte, eosinophil, and NLR levels were statistically significantly higher in patients in the severe group than the mild group ($p<0.001$). In ROC analysis, the area under the characteristic curve (AUC) for CRP, monocyte, neutrophils, eosinophil, and NLR was calculated as 0.574, 0.569, 0.601, 0.628, and 0.583, respectively and all found statistically significant ($p<0.001$). Correlation analysis revealed that CRP had a positive correlation with neutrophil count ($r=0.231$, $p=0.011$) and NLR ($r=0.221$, $p=0.015$) in the severe COP patients.

Conclusion: Increased neutrophils, eosinophil, monocytes, CRP, and NLR, were predicting the severity of CAP. NLR and neutrophils had a significant correlation with CRP and potential parameters for evaluating the severity of CAP disease.

Keywords: Community-acquired pneumonia, children, neutrophils, neutrophil-to-lymphocyte ratio, monocyte, eosinophil, diagnostic value

INTRODUCTION

Community-acquired pneumonia (CAP) is a significant and common cause of hospitalization in children (1, 2). In developing countries, hospitalization for childhood CAP accounts for 8.7% of all hospitalizations and accounts for approximately 19% of all deaths in children below the age of five (3). Because CAP can cause mild to severe illness, it continues to cause an increasing rate of complications and fatality, despite the advancement of new therapeutic interventions (4). The greatest difficulty for a clinician is risk determination of children with CAP; thus, therefore, earlier risk detection is important to reduce mortality and morbidity.

Leucocyte count, erythrocyte sedimentation rate, and C-reactive protein (CRP) widespread utilized with chest X-ray for diagnosis, treatment planning, identifying patients at risk and evaluating progression of CAP. Their specificity and sensitivity for forecasting CAP severity, even so, are changeable and primarily not enough (4). As a result, more screening tests are speedily required to determine disease severity and clarify the diagnostics. While these tests are being developed, it is critical that they are affordable and easily accessible so that they can be used in less developed countries where CAP is most prevalent.

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Complete blood count (CBC) markers; such as platelets, monocyte, lymphocytes, neutrophils, as well as the red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW) platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) have been suggested as predictors of infection and inflammation in variety of diseases (5-8). Although there are few studies in adults on the importance of blood parameters in CAP, there are almost none in children (4,9).

As a result, this research analyzed the clinical and laboratory characteristics of 400 children with CAP and looks back at platelet, monocyte, lymphocyte, neutrophil, eosinophil, RDW, PDW, MPV, PLR, and NLR levels in CAP patients to assess their clinical utility and connection with disease severity.

MATERIAL AND METHOD

The study was carried out with the permission of Health Science University Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 9.11.2021, Decision No: 2012-KAEK-15/2416). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. With the ethics committee approval, the data were scanned retrospectively using the Hospital Information Management System.

A retrospective, cross-sectional study included children aged 3 months to 18 years who diagnosed with CAP at Ankara Atatürk Sanatorium Training and Research Hospital's pediatrics clinics between January 2018 and June 2021, as well as age-matched healthy children. CAP case definition was made according to the community-acquired pneumonia case definition defined by the World Health Organization (WHO):

- Any child presenting with cough or difficulty breathing;
- Tachypnea >40/min (12-59 months); >30/min (≥60 months);
- Abnormal chest X-ray findings accompanying drawling findings (consolidation or perihilar infiltration) with or without wheezing (10).

The presence of severe disease will be determined according to WHO and British Thoracic Society 2011 guidelines (11, 12). Patients with underlying chronic disease, a history of recent hospitalization, and suspected hospital-acquired infection did not be included in the study. The control group will consist of healthy children aged between 3 months and 18 years, without chronic inflammatory disease, blood disease, and acute infection.

Data on the patient age, gender, clinical features, CBC and CRP were collected: CBC was performed using the ADVIA 2120 Hematology System (Siemens Healthcare Diagnostics, Erlangen, Germany). A radiologist evaluated the patients' chest radiographs, which were derived from the hospital's dataset, for the existence of indications promoting a diagnosis of CAP. All variables were compared between groups.

Statistical Analyses

SPSS for Windows, version 22.0, was used to analyze the data (SPSS Inc., Chicago, IL, United States). The Kolmogorov Smirnov test was used to determine whether the distribution of continuous variables was normal or not. The Levene test was used to assess variance homogeneity. For skewed distributions, continuous data were described as mean SD and median (Q1: first quartile - Q3:third quartile). The number of cases (%) was used to describe categorical data. The Mann Whitney U test was used to compare differences in not normally distributed variables between two independent groups. Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. On all statistical analyses, the p-value of 0.05 was accepted as the significant level. The cutoff values for CRP, monocytes, neutrophils, eosinophil, and NLR associated with the risk of severe disease were determined using ROC curve analysis. It was evaluated degrees of relation between variables with Spearman Correlation analysis.

RESULTS

400 CAP patients and 400 control patients were included in the study. The mean and median age of the CAP group was 2.40±3.20 years and 0.93 (0.33-3.29) years, respectively. The mean and the median age of control group were 2.38±3.17 years and 0.93 (0.32-3.24) years, respectively. There was no statistically significant difference between the ages of CAP and control group (p=0.926). 62% of CAP patients were male and 38% female. There was no statistically significant difference between the CAP and control group in terms of gender (p=0.999). The mean hospitalization length was 5.27±1.94 days in CAP patients. 121 (30.3%) of CAP patients had severe disease while 279 (69.7%) had mild disease. Recurrent pulmonary infections were present in 88 (22%) of the total CAP patients. 36.4% of severe CAP patients and 15.8% of mild CAP patients had recurrent pulmonary infections. The most common symptoms were cough (97.8%), wheeze (64.5%), and fever (41.8%). Feeding difficulties (25.0%), diarrhea (14.2%), nasal congestion (13.0%), restlessness (8.0%), vomiting (4.3%), abdominal pain (3.0%), hoarseness (2.0%) and febrile seizure (1.0%) were other first application symptoms. The most common findings observed in patients' initial physical examinations were rhonchi (71.8%), tachypnea (69.5%) and wheezing (64.5%) followed by tachycardia (50.2%), respiratory

distress (46.3%), SpO_2<%90 (32.3%), rales (35.3%), skin rash (5.0%), shock (2.0%), cyanosis (4.0%), dehydration (1.0%), lethargy (1.0%) , and conjunctivitis (1.0%). The most common finding in posterior-anterior chest X-Ray was paracardiac infiltration (49.5%), followed by reticular and (38.5%) lobar infiltration (5.0%). Rotavirus (5.3%) and Influenza were (5%) accompanying viral infections. 35.3% of CAP patients got oxygen treatment with mask or nasal cannula, 3.0% with airvo, none of the patients needed mechanical ventilation. Antibiotic treatments applied to the patients were: clarithromycin (66.8%), sulbactam ampicillin (41.5%), oseltamavir (40.3%), ceftriaxone (33.5%), cefotaxime (19.0%), and vancomycin (5.0%). Inhaled salbutamol was given to 78.8% of patients inhaled budesonide 31%. Dexamethasone was given 37.3% of the patients.

Eosinophil, hemoglobin, mean platelet volume (MPV), platelet distribution width (PDW) and PLR values of CAP group was statistically significantly lower than the control group (p<0.05). Leukocyte, lymphocyte, monocyte, neutrophil, basophil, platelet, red cell distribution width (RDW), NLR levels of CAP group was statistically significantly higher than the control group (p<0.05) (**Table 1**).

The mean age of the severe group was 2.92±3.80, while it was 2.17±2.88 in the mild group. There was no statistically significant difference in age between severe and mild groups (p>0.05). The ratio of males in severe group (80.2%) was statistically significantly higher than mild (54.1%) group (p<0.001) (**Table 2**). The mean hospitalization length in severe group (6.16±2.00 days) was statistically significantly higher than mild (4.89±1.78 days) group (p<0.001). Recurrent pulmonary infections were statistically significantly higher in severe group (36.4%) than mild (15.8%) group (p<0.001). Vomiting and abdominal pain symptoms were statistically significantly higher in mild group than severe group (p<0.001). Wheeze, restlessness, febrile convulsion and feeding difficulty symptoms were statistically significantly higher in severe group than mild group (p<0.001). In the physical examination, rhonchi, wheezing, tachypnea, respiratory distress, low oxygen saturation (SpO_2<90%), cyanosis, tachycardia and lethargy were statistically significantly high in severe group than in mild group (p<0.001). In the physical examination, skin rash was statistically significantly high in mild group than in severe group (p<0.001). Oxygen treatment with nasal/mask and airvo was statistically significantly high in severe group than in mild group (p<0.001). In severe group, antibiotic treatments included cefotaxime, clarithromycin, vancomycin, and oseltamavir; rates of salbutamol, budesonide inhaler treatments, and intro venous dexamethasone treatment were statistically significantly higher (p<0.001) (**Table 2**). CRP, neutrophils, monocyte, eosinophil, and NLR levels were statistically significantly high in patients with severe group than mild group (p<0.001) (**Table 3**).

In ROC analysis, the area under the characteristic curve (AUC) for CRP, monocyte, neutrophils, eosinophil, and NLR was calculated as 0.574, 0.569, 0.601, 0.628, and 0.583, respectively (**Figure 1**). CRP, neutrophils, monocyte, eosinophil and NLR were found to be statistically significant (p<0.001). This finding suggests that CRP, neutrophils, monocyte, eosinophil, and NLR levels can be used to screen for severe disease. The best cut-off point for CRP was calculated to be 10.85, with 53.7% sensitivity and 62.7% specificity. The best cut-off point for monocyte was 0.79, with a sensitivity of 66.9% and a specificity of 58.3%. A cut-off value of 9.31 was calculated for neutrophils with a sensitivity of 33.9% and a specificity of 88.2%. The best cut-off point for eosinophil was calculated as 0.16 with 57% sensitivity and 72% specificity. The best cut-off point for NLR was calculated to be 1.68, with 50.4% sensitivity and 68.3% specificity (**Table 4**).

Table1. Comparison of the laboratory findings of patients with community-acquired pneumonia and controls.

	Community-acquired Pneumonia Group (n:400)	Control Group (n:251)	p
	$\bar{x}$ ± SD Med (Min-Max)	$\bar{x}$ ± SD Med (Min-Max)	
CRP (mg/L)	19.66±29.36 8.02 (2.29-20.00)	-	-
Leukocytes ($\times10^3$/μL)	11.95±4.66 11.20 (8.70-13.50)	7.31±1.84 7.09 (6.02-8.60)	<0.001
Lymphocytes ($\times10^3$/μL)	4.60±2.84 4.15 (2.24-6.39)	2.94±0.87 2.84 (2.24-3.56)	<0.001
Monocyte ($\times10^3$/μL)	0.89±0.72 0.79 (0.56-1.06)	0.49±0.19 0.44 (0.36-0.55)	<0.001
Neutrophils ($\times10^3$/μL)	6.21±4.48 4.93 (3.42-8.43)	3.73±1.34 3.69 (2.61-4.63)	<0.001
Eosinophil ($\times10^3$/μL)	0.18±0.22 0.08 (0.02-0.30)	0.21±0.18 0.15 (0.08-0.26)	<0.001
Basophile ($\times10^3$/μL)	0.29±2.26 0.03 (0.02-0.04)	0.07±0.15 0.03 (0.02-0.06)	<0.001
Hemoglobin (g/dL)	11.57±1.83 11.50 (10.60-12.60)	13.43±0.91 13.60 (12.90-14.00)	<0.001
RDW (%)	15.12±2.74 14.00 (13.50-15.80)	14.13±1.63 13.70 (12.95-15.10)	<0.001
Platelet ($\times10^3$/μL)	383.07±129.32 362.00 (297.00-451.00)	296.07±63.05 287.94 (252.48-330.67)	<0.001
MPV (fL)	8.48±0.87 8.40 (7.80-9.10)	8.94±1.60 9.18 (7.60-10.18)	<0.001
PCT (%)	3.24±1.04 3.10 (2.40-3.90)	-	<0.001
PDW (%)	15.57±0.40 15.50 (15.30-15.80)	16.38±1.32 16.20 (15.70-16.90)	<0.001
PLR	119.24±82.59 91.36 (63.96-143.21)	107.66±31.82 104.53 (85.08-33.33)	0.007
NLR	2.48±3.19 2.15 (0.57-3.34)	1.39±0.66 1.33 (0.84-1.93)	0.006

*CRP: C-reactive protein; MPV: Mean Platelet Volume, PDW: Platelet Distribution Width; RDW: Red Cell Distribution Width; NLR: Neutrophil to Lymphocyte Ratio;; PLR: Platelet to Lymphocyte Ratio

Table 2. Comparison of the demographic and clinical features of patients with severe and mild community-acquired pneumonia

	Community acquired pneumonia patients (n:400)		p
	Severe (n:121) $\bar{x}$± SD Med (Min-Max)	Mild (n:279) $\bar{x}$± SD Med (Min-Max)	
Age (years)	2.92±3.80 1.18 (0.25-4.30)	2.17±2.88 0.93 (0.33-3.08)	0.366
Gender			<0.001
Male	97 (80.2%)	151 (54.1%)	
Female	24 (19.8%)	128 (45.9%)	
Length of hospitalization (days)	6.16±2.00 6 (4-8)	4.89±1.78 5 (4-6)	<0.001
Recurrent pulmonary infection (%)	44 (36.4%)	44 (15.8%)	<0.001
Symptoms (%)			
Cough	117 (96.7%)	161 (57.7%)	<0.001
Wheeze	97 (80.2%)	274 (98.2%)	0.463
Fever	53 (43.8%)	114 (40.9%)	0.584
Nasal congestion	16 (13.2%)	36 (12.9%)	0.930
Hoarseness	0 (0.0%)	8 (2.9%)	0.112
Restlessness	16 (13.2%)	16 (5.7%)	0.011
Vomiting	0 (0.0%)	17 (6.1%)	0.006
Febrile seizure	4 (3.3%)	0 (0.0%)	0.008
Abdominal pain	12 (0.0%)	12 (4.3%)	0.021
Feeding difficulty	56 (46.3%)	44 (15.8%)	<0.001
Diarrhea	12 (9.9%)	45 (16.1%)	0.103
Physical Examination (%)			
Rales	36 (29.8%)	93 (33.3%)	0.482
Rhonchi	97 (80.2%)	190 (68.1%)	0.014
Tachypnea	117 (96.7%)	161 (57.7%)	<0.001
Wheezing	97 (80.2%)	161 (57.7%)	<0.001
Respiratory distress	117 (96.7%)	68 (24.4%)	<0.001
Cyanosis	8 (6.6%)	0 (0.0%)	<0.001
SpO_2<%90	109 (90.1%)	32 (11.5%)	<0.001
Tachycardia	117 (96.7%)	84 (30.1%)	<0.001
Dehydration	4 (1.4%)	0 (0.0%)	0.320
Shock	4 (1.4%)	0 (0.0%)	0.320
Lethargy	4 (3.3%)	0 (0.0%)	0.008
Skin rash	0 (0.0%)	20 (7.2%)	0.003
Conjunctivitis	0 (0.0%)	4 (1.4%)	0.320
Posterior-anterior Chest X-Ray (%)			
Reticular infiltration	52 (43.0%)	102 (36.6%)	0.226
Para cardiac infiltration	65 (53.7%)	133 (47.7%)	0.266
Lobar infiltration	4 (3.3%)	16 (5.7%)	0.306
Accompanying viral infection (%)			
Rotavirus	8 (6.6%)	13 (4.7%)	0.421
Influenza	8 (6.6%)	12 (4.3%)	0.330
O_2 treatment (%)			
With mask or nasal cannula	109 (90.1%)	32 (11.5%)	<0.001
With airvo	12 (9.9%)	0 (0.0%)	<0.001
Medical treatment (%)			
Ceftriaxone (i.v.)	36 (29.8%)	98 (35.1%)	0.296
Cefotaxime (i.v.)	32 (26.4%)	44 (15.8%)	0.012
Sulbactam ampicillin (i.v)	49 (40.5%)	117 (41.9%)	0.788
Clarithromycin (i.v.)	109 (90.1%)	158 (56.6%)	<0.001
Vancomycin (i.v.)	16 (13.2%)	4 (1.4%)	<0.001
Oseltamivir (p.o)	60 (49.6%)	101 (36.2%)	0.012
Salbutamol (inh)	109 (90.1%)	206 (73.8%)	<0.001
Budesonide (inh)	76 (62.8%)	48 (17.2%)	<0.001
Dexamethasone (i.v.)	93 (76.9%)	56 (20.1%)	<0.001

i.v. : intravenosus, inh: inhaler

Table 3. Comparison of laboratory findings of patients with severe and mild community-acquired pneumonia

	Community acquired pneumonia patients (n:400)		p
	Severe (n:121)	Mild (n:279)	
	x-± SD Med (Min-Max)	x-± SD Med (Min-Max)	
CRP (mg/L)	23.05±31.13 11.19(3.45-28.60)	18.14±28.45 7.50(1.97-19.95)	0.019
Leukocytes (×10³/μL)	12.50±4.37 11.50(9.30-15.10)	11.72±4.77 11.10(8.70-13.20)	0.063
Lymphocytes (×10³/μL)	4.44±2.83 3.85(2.29-5.33)	4.68±2.85 4.23(2.14-6.39)	0.358
Monocyte (×10³/μL)	0.87±0.36 0.83(0.68-1.10)	0.90±0.83 0.74(0.49-1.06)	0.035
Neutrophils (×10³/μL)	6.90±4.09 5.74(3.91-9.51)	5.91±4.62 4.62(2.92-7.69)	0.002
Eosinophil (×10³/μL)	0.22±0.20 0.20(0.04-0.42)	0.16±0.22 0.06(0.02-0.19)	<0.001
Basophile (×10³/μL)	0.13±0.53 0.03(0.02-0.04)	0.36±2.69 0.03(0.02-0.05)	0.052
Hemoglobin (g/dL)	11.85±2.02 11.50(10.20-12.90)	11.44±1.73 11.50(10.60-12.20)	0.269
RDW (%)	15.21±3.01 13.90(13.50-15.50)	15.07±2.62 14.00(13.50-16.30)	0.832
Platelet (×10³/μL)	377.72±104.24 345.00(299.00-430.00)	385.39±138.90 364.00(291.00-451.00)	0.916
MPV (fL)	8.48±0.83 8.30(7.80-9.10)	8.49±0.88 8.50(7.80-9.10)	0.728
PCT (%)	3.18±0.80 3.10(2.50-3.70)	3.26±1.13 3.10(2.30-3.90)	0.755
PDW (%)	15.52±0.35 15.40(15.30-15.70)	15.60±0.42 15.50(15.30-15.80)	0.189
PLR	124.66±90.95 92.27(73.36-143.75)	116.89±78.75 91.36(63.96-142.86)	0.480
NLR	2.76±3.09 1.70(0.71-3.94)	2.36±3.23 1.02(0.55-2.93)	0.009

*CRP: C-reactive protein; MPV: Mean Platelet Volume, PDW: Platelet Distribution Width; RDW: Red Cell Distribution Width; NLR: Neutrophil to Lymphocyte Ratio;; PLR: Platelet to Lymphocyte Ratio

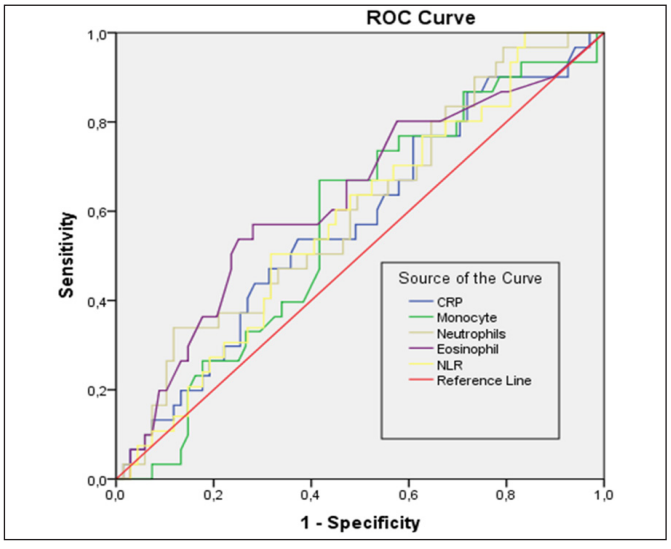

Figure 1. ROC curve was used to evaluate the diagnostic value of CRP, neutrophil, monocyte, eosinophil, and NLR

Correlation analysis revealed that CRP had a positive correlation with neutrophil count (r=0.231, p=0.011) and NLR (r=0.221, p=0.015) in severe COP patients (**Figure 2**).

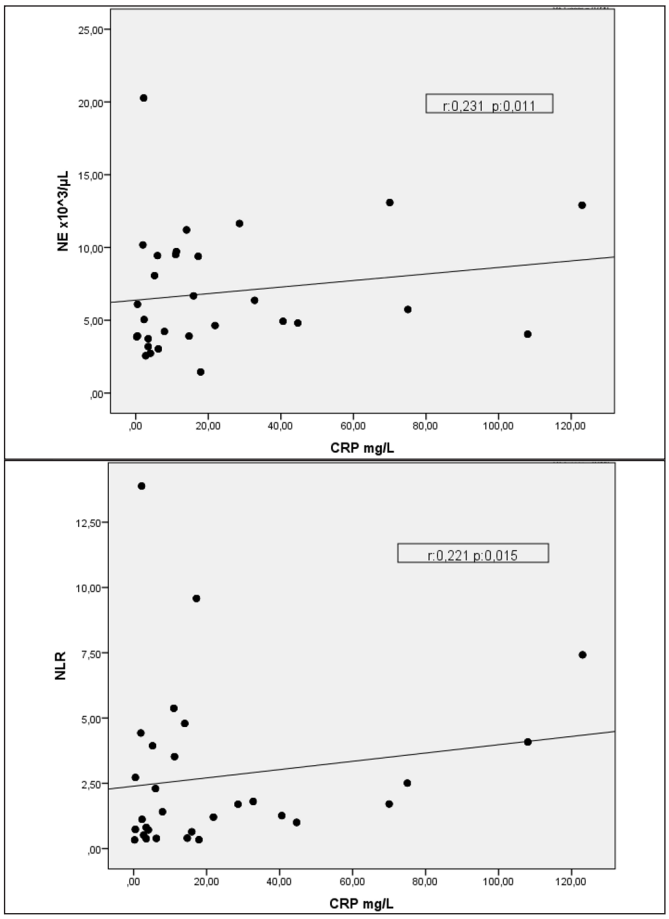

Figure 2. Significant correlation between CRP and neutrophils (r=0.231, p=0.011) and, CRP and NLR (r=0.221, p=0.015) in Spearman Correlation Analysis.

DISCUSSION

CAP continues to cause a high rate of complications and death, notwithstanding the sudden innovation of unique treatment options. Further, simple and low cost screening tests are desperately required to determine disease severity and clarify treatment plan. For this purpose, we have brought a new perspective that can help the classification of CAP severity in children by using complete blood parameters. The major results of our research were that platelets, leukocytes, lymphocytes, monocyte, neutrophils, RDW and NLR levels were significantly higher in CAP than in the control group

Table 4. ROC curve was used to evaluate the diagnostic value of blood parameters for severe community-acquired pneumonia

	AUC	p	Asymptotic	95% Confidence Interval	Cut-Off	Sensitivity	Specificity
CRP	0.574	0.019	0.513	0.635	10.85	53.7%	62.7%
Monocyte	0.569	0.030	0.509	0.628	0.79	66.9%	58.3%
Neutrophils	0.601	0.001	0.541	0.660	9.31	33.9%	88.2%
Eosinophil	0.628	<0.001	0.567	0.689	0.16	57.0%	72.0%
NLR	0.583	0.009	0.524	0.642	1.68	50.4%	68.3%

while hemoglobin, eosinophil, PDW, MPV and PLR levels lower. However, when disease severity was considered, neutrophils, monocytes, eosinophil, CRP, and NLR levels were found to be statistically significantly higher in the severe group. In the ROC analysis, we showed that these values can be used to differentiate severe disease. A significant positive correlation was discovered in the correlation analysis between CRP and NLR, as well as between CRP and neutrophil levels.

CRP is an effective indicator that stimulates cytokine production in eight to twelve hours of inflammatory process and is unaffected or only mildly affected by gender and age so it is frequently utilized in the diagnosis and follow-up of acute infection (13). CRP is reported in the literature to be a much specific and sensitive indicator for CAP (14,15). In our study, we found that CRP had a predictive value for both CAP diagnosis and severity.

Neutrophils and lymphocytes were demonstrated to be shown to play critical roles in inflammatory conditions. It has been reported that the increase in neutrophils and again decrease in lymphocytes in CAP patients is associated with disease severity (16). Elevated neutrophils were associated with disease severity in our study; however we did not found a link between lymphocytes.

NLR is a parameter determined by the ratio of neutrophils to lymphocytes. NLR is recognized to enhance inflammatory process and thought to be a forecaster of several inflammation process better than CRP (17). In some studies NLR was reported to be an important marker, particularly for hospitalized children with CAP (18-21). Neutrophils and NLR values together were reported a stronger predictor of severity than pneumonia severity score and the tenacity of high levels of NLR with neutrophils count might be a crucial factor in the rapidly deteriorating of patient's poor outcome (16,22,23). Continuous elevations in these variables might well indicate a severe and unmanaged immune reaction, causing the inability to fix the systemic inflammation process. Similar to these studies, NLR and neutrophil count were found to be elevated in severe disease, significantly predicting disease severity and positively correlated with CRP in our study.

Monocytes can differentiate into a variety of irredeemably distinguishable cells that can execute a wide range of functions throughout infection. They can boost microbicidal activity. Monocyte levels were reported to be increased in CAP patients (4). Similar to previous studies, the monocyte level was found to be statistically significantly higher in the CAP patient group than in the control group in our study. However, in addition to previous research, we discovered that it was elevated in severe CAP and predicted disease severity.

Eosinopenia is commonly associated with acute stress or infection responses (24). There have been very few studies on the relationship between CAP and eosinophilia, and the majority of them have been conducted on adults with chronic disease. In some of them, the presence of eosinopenia was found to be associated with the severity of CAP (25), but not in others (26). Eosinophil counts were found to be statistically significant lower in CAP patients compared to the control group in our study. The eosinophil count, on the other hand, was found to be significantly higher in the severe CAP group compared to the mild group, and the increase in eosinophil count was found to be associated with disease severity. The reason for this could be that the etiological factors of CAP in children differ from those in adults. At the same time, because eosinophil counts are high in children with reactive airway disease who can develop severe pneumonia, we may have detected higher eosinophil counts in severe patients.

Platelets are essential inflammation cells that generate a big portion of cytokines and also can behave as acute phase reactants as well. Platelet counts were reported to be higher in children with pneumonia (27, 28). Similarly we found statistically significant increase in platelet counts of CAP patients than controls. On the other hand; we did not find an association between platelet counts and CAP severity.

MPV and PDW are two key platelet markers associated with inflammation. MPV and PDW levels in pneumonia patients were lower than in the control group in our study, as previously reported (2,27-30). The level of MPV was reported to decrease with the severity of the pneumonia however we did not find an association between MPV and CAP severity.

PLR levels were found to be elevated in CAP patients (4,18,31,32). While PLR has been linked to disease severity in some studies (4,32,33), it has not been found in others (4,18). In another study, children with bacterial infectious pneumonia had significantly lower PLR values than healthy children (33). PLR was found to be significantly lower in the CAP group compared to the control group in our study, and no correlation was found between PLR and disease severity. Due to the retrospective nature of our study, the causative agent could not be determined because most of the patients' blood culture results could not be obtained. Therefore, we cannot say that we found low PLR levels due to higher bacterial pneumonias.

RDW, which is an indicator of anisocytosis, is a measurement that is reported in total blood cell counts. RDW has been used primarily to determine

the type of anemia and for diagnosis. The RDW index is now regarded as a crucial measure of the level of inflammation. In CAP, high RDW values have been linked to a poor prognosis (31,34,35). Although the RDW level was found to be statistically significantly higher in the CAP patient group than in the control group in our study, no correlation with disease severity was found.

Our study had some limitations: it was a single-center study, and we did not investigate the effect of treatment on these serum inflammatory parameters due to a lack of data; additionally, the causative agent could not be determined because most of the patients' blood culture results could not be obtained. To validate, additional controlled studies with a larger number of patients from various centers are required.

CONCLUSION

According to the findings of this study, platelets, leukocytes, neutrophils, lymphocytes, monocytes, RDW, CRP, and NLR were elevated in CAP patients while hemoglobin, eosinophil, PDW, MPV and PLR were decreased, indicating a diagnostic value for CAP. Elevation in neutrophils, eosinophil, monocytes, CRP, and NLR, were predicting the severity of CAP. NLR and neutrophils had a significant correlation with CRP for severe disease. These parameters have the potency to be a credible, cost-effective, and unique potential parameter for diagnosing and assessing the severity of CAP disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University, Keçiören Training and Research Hospital Clinical Research Ethics Committee (Date: 9.11.2021, Decision No: 2012-KAEK-15/2416).

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. DeFrances CJ, Lucas CA, Buie VC, Golosinskiy A. 2006 national hospital discharge survey. Natl Health Stat Report 2008; 5: 1-20.
2. Karadag-Oncel E, Ozsurekci Y, Kara A, Karahan S, Cengiz AB, Ceyhan M. The value of mean platelet volume in the determination of community acquired pneumonia in children. Ital J Pediatr 2013; 39: 16.
3. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ 2008; 86:408-16.
4. Huang Y, Liu A, Liang L, et al. Diagnostic value of blood parameters for community-acquired pneumonia. Int Immunopharmacol 2018; 64: 10-5.
5. Ramby AL, Goodman DM, Wald EL, Weiss SL. Red Blood Cell Distribution Width as a Pragmatic Marker for Outcome in Pediatric Critical Illness PLoS One 2015; 10: e0129258.
6. Golwala ZM, Shah H, Gupta N, Sreenivas V, Puliyel JM. Mean platelet volume (MPV), platelet distribution width (PDW), platelet count and plateletcrit (PCT) as predictors of in-hospital paediatric mortality: a case-control Study Afr Health Sci 2016; 16: 356-62.
7. Gul A, Takçı Ş, Seyyah BA, Yılmaz R. Independent predictors of severity and hospitalization in acute bronchiolitis: neutrophil/lymphocyte ratio and mean platelet volume. J Pediatr Infect Dis 2018; 13: 268-73.
8. Zhang S, Luan X, Zhang W, Jin Z. Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratio as predictive biomarkers for early-onset neonatal sepsis. J Coll Physicians Surg Pak 2021; 30: 821-4.
9. Pantzaris ND, Platanaki C, Pierrako C, et al. Neutrophil-to-lymphocyte ratio relation to sepsis severity scores and inflammatory biomarkers in patients with community-acquired pneumonia: a case series. J Transl Int Med 2018; 6: 43–6.
10. World Health Organization. The Management of Acute Respiratory Infections in Children. Practical Guidelines for Outpatient Care. Geneva: World Health Organization; 1995.
11. World Health Organization. Pocket Book of Hospital Care for Children. Guidelines for the Management of Common Illnesses with Limited Resources.WHO Press 2005:72–81.
12. Harris M, Clark J, Coote N, et al. British Thoracic Society Standards of Care Committee. British Thoracic Society guidelines for the management of community acquired pneumonia in children. Thorax 2011; 66: 1–23.
13. Litao MK, Kamat D. Erythrocyte sedimentation rate and C-reactive protein: how best to use them in clinical practice. Pediatr Ann 2014; 43: 417–20.
14. Berg AS, Inchley CS, Fjaerli HO, Leegaard TM, Lindbaek M, Nakstad B. Clinical features and inflammatory markers in pediatric pneumonia: a prospective study. Eur J Pediatr 2017; 176: 629–38.
15. Khan DA, Rahman A, Khan FA. Is procalcitonin better than C-reactive protein for early diagnosis of bacterial pneumonia in children? J Clin Lab Anal 2010; 24:1–5.
16. Curbelo J, Bueno SL, Galván-Román JM, Ortega-Gomez M, Rajas O, Fernandez-Jimenez G. Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: Importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio. PLoS One 2017; 12: e0173947.
17. de Jager CP, Wever PC, Gemen EF, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. PloS One 2012; 7:e46561.

18. Kartal O, Kartal AT. Value of neutrophil to lymphocyte and platelet to lymphocyte ratios in pneumonia. Bratisl Lek Listy 2017; 118: 513–6.
19. Bekdas M, Goksugur SB, Sarac EG, Erkocoglu M, Demircioglu F. Neutrophil/lymphocyte and C-reactive protein/mean platelet volume ratios in differentiating between viral and bacterial pneumonias and diagnosing early complications in children. Saudi Med J 2014; 35: 442–7.
20. Bekis BH. Is there any relationship between C-reactive protein/albumin ratio and clinical severity of childhood community-acquired pneumonia. Turk J Biochem 2021; 46, 647-53.
21. Najm RA, AL-dujaili ANG, Hashim JM. Study of procalcitonin and neutrophil/ lymphocyte count ratio in children infected with Community-acquired pneumonia. Int J Health Sci 2022; 6: 4218–32.
22. Fernandes CD, Arriaga MB, Costa MCM, et al. Host inflammatory biomarkers of disease severity in pediatric community-acquired pneumonia: a systematic review and meta-analysis. Open Forum Infect Dis 2019; 6:ofz520.
23. Yang T, Wan C, Wang H, et al. The prognostic and risk-stratified value of neutrophil-lymphocyte count ratio in Chinese patients with community-acquired pneumonia. Eur J Inflamm 2017; 15: 22-7.
24. Abidi K, Khoudri I, Belayachi J, et al. Eosinopenia is a reliable marker of sepsis on admission to medical intensive care units. Crit Care 2008, 12: R59.
25. Huang WC, Lee CH, Wu MF, et al. Clinical features, bacteriology of endotracheal aspirates and treatment outcomes of patients with chronic obstructive pulmonary disease and community-acquired pneumonia in an intensive care unit in Taiwan with an emphasis on eosinophilia versus non-eosinophilia: a retrospective case-control study. BMJ open 2018; 8, e020341.
26. Perelló R, Miró O, Ma Miró J, Moreno A. Role of the eosinophil count in discriminating the severity of community-acquired pneumonia in HIV-infected patients. Critical Care 2008; 12: 425.
27. Sahin M, Duru NS, Elevli M, Civilibal M. Assessment of platelet parameters in children with pneumonia. J Pediatr Infect 2017; 11: 106-12.
28. Choudhury J, Rath D. Thrombocytosis in under-five children with lower respiratory tract infection. Arch Pediatr Infect Dis 2018; 6: e61605.
29. Afyon M, Artuk C. Could mean platelet volume be a useful marker for infectious diseases? a review of literature. Med Sci 2016; 5: 1059-62.
30. Robbins G, Barnard DL. Mean platelet volume change in infection. J Clin Pathol 1983; 36: 1320.
31. Qi X, Dong Y, Lin X, Xin W. Value of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and red blood cell distribution width in evaluating the prognosis of children with severe pneumonia. Evid Based Complement Alternat Med 2021: 1818469.
32. Bolatkale M. Toplumda gelişen pnömoninin öngörülmesinde trombosit-lenfosit oranı ve pnömoni ağırlık skorunun karşılaştırılması. Dokuz Eylül Üniversitesi Tıp Fakültesi Derg 2018; 32: 191-200.
33. Zheng HH, Xiang Y, Wang Y, Zhao QS, Fang R, Dai R. Clinical value of blood related indexes in the diagnosis of bacterial infectious pneumonia in children. Transl Pediatr 2022; 11:114-9.
34. Bello S, Fandos S, Lasierra AB, et al. Red blood cell distribution width [RDW] and long-term mortality after community-acquired pneumonia. a comparison with proadrenomedullin. Respir Med 2015; 109: 1193–206.
35. Lee S-M, Lee JH, Kim K, et al. The clinical significance of changes in red blood cell distribution width in patients with community-acquired pneumonia. Clin Exp Emerg Med 2016; 3: 139–47.

Original Article

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Comparison of the effects of ultrasound-guided thoracic paravertebral block and erector spinae plane block on postoperative acute and chronic pain in patients undergoing video-assisted thoracoscopic surgery

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ABSTRACT

Aim: The aim of the study was to compare the effects of ultrasound (US)-guided Erector spinae plane block (ESPB) and thoracic paravertebral block (TPVB) on postoperative acute and chronic pain.

Material and Method: Patients aged range of 18 to 80 years and underwent video-assisted thoracoscopic surgery (VATS) were included in a single-blinded randomized trial. All patients were informed about the study and their written consent was obtained. The primary outcome was determined as acute postoperative visual analog scale (VAS) scores, and secondary outcomes were postoperative morphine consumption and the incidence of chronic pain. US-guided ESPB and TPVB were performed to all patients and they were assigned randomly to ESPB (Group 1) and TPVB (Group 2) groups according to the analgesia protocol.

Results: Visual analog scale (VAS) resting and VAS cough scores at the 1st, 2nd, 4th, 8th, and 16th hours were found to be statistically significantly higher in the TPVB group than in the ESPB group ($p<0.05$) Morphine consumption (p:0.042) and additional analgesic (p:0.037) use were found to be statistically significantly higher in the TPVB group compared to the ESPB group. As complications, only nausea and vomiting were observed with no significant difference between the groups ($p>0.05$). There was no significant difference in terms of postoperative 30th and 90th day pain characteristics between the groups ($p>0.05$).

Conclusion: ESPB was superior to TPVB in terms of acute postoperative pain management, morphine consumption, and side effects, but the incidence of chronic pain in the first and third months after surgery was similar in both groups.

Keywords: Acute pain, chronic pain, erector spinae plane block, thoracic paravertebral block, video-assisted thoracoscopic surgery

INTRODUCTION

In thoracic surgery, video-assisted thoracoscopic surgery (VATS) procedures are gaining popularity due to the minimally invasive approach resulting in limited tissue trauma, shorter recovery time, and lesser postoperative pain (1,2). Even though VATS is less invasive than open thoracotomy, moderate to severe acute pain is common after VATS, and is also associated with significant chronic pain (1,3).

In the early postoperative period, poorly managed acute pain has significant adverse effects on respiratory mechanics and mobilization and increased risk of postoperative pulmonary complications (4).

The mechanism of chronic pain after thoracic surgery is still under debate. One of the possible mechanisms of chronic pain is intercostal nerve damage during surgery. Previous studies have shown chronic pain in 40% to 80% of patients after thoracotomy and in 20% to 40% after VATS (5).

Thoracic epidural analgesia (TEA) remains the gold standard in the treatment of postoperative pain in thoracic surgery (6-8). However, TEA may cause side effects such as hypotension, urinary retention, nausea, and vomiting (8,9).

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Therefore, in recent years, peripheral blocks have been preferred more for postoperative analgesia following VATS applications. There are also studies showing that peripheral blocks and TEA provide similar postoperative analgesia after VATS (7,8,10).

Thoracic paravertebral block (TPVB) has been employed to prevent postoperative pain after thoracic surgery (11). Erector spinae plane block (ESPB), a novel plane block first introduced by Forero et al. (12) in 2016, provide analgesia for different surgeries such as lung surgery, laparoscopy, mastectomy, and pediatric surgery, and may also be effective for the management of chronic pain (12). The possible mechanism of action of ESPB is related to the distribution of the local anesthetic solution into the paravertebral and epidural space (13) and subsequently blocking the dorsal and ventral branches of the spinal nerve. Although many studies have been conducted on the effectiveness of ESPB in the prevention of acute pain after VATS, studies evaluating its effects on chronic pain are very limited.

We hypothesized that the application of ESPB before surgical incision may prevent acute and chronic pain after VATS. In this study, the primary outcome was determined as acute postoperative visual analog scale (VAS) scores, and secondary outcomes were postoperative morphine consumption and the incidence of chronic pain. Our aim is to compare the effects of ultrasound-guided ESPB and TPVB on postoperative acute and chronic pain.

MATERIAL AND METHOD

Study Design and Patients

The study was carried out with the permission of Ankara Keçiören Training and Research Hospital Ethics Committee (Date:13.04.2021, Decision No: 2012-KAEK-15:2232). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was conducted with a prospective, randomized, single-blind design.

The VATS patients, in the age range of 18 to 80 years, with the American Society of Anesthesiologists (ASA) physical status 1-3 and body mass index (BMI) of 18-30 kg/m² were included in the study. In a high-volume tertiary thoracic surgery center, patients were informed about the study, and their written consent was obtained. During the preoperative evaluation, the patients were informed about pain assessment and patient-controlled analgesia (PCA). Patients with preoperative acute or chronic pain and a history of opioid therapy were excluded. Moreover, patients with bleeding disorders, infection at the injection site, or allergy to local anesthetics and patients who underwent emergency surgery, and conversion to thoracotomy were excluded from the study.

Patients were assigned to ESPB (Group 1) and TPVB (Group 2) groups according to the analgesia protocol. 71 patients were included in the study. Randomization was performed using computer-generated random numbers. Blinding was performed by concealing information in closed opaque envelopes.

General anesthesia

Patients were monitored in the operating room in accordance with the ASA standards. Patients were administered 0.03 mg/kg midazolam for premedication. Following preoxygenation, anesthesia was induced with 2 mg/kg propofol, 1.5 mcg/kg fentanyl, and 0.1 mg/kg vecuronium. After the intubation with a left-sided double-lumen endobronchial tube, anesthesia was maintained by administering sevoflurane in oxygen and air mixture and by administering remifentanil infusion at a dose of 0.01-0.20 mcg/kg/min. Before the commencement of the surgical procedure, blocks were performed under ultrasonography (US) guidance.

Block procedures

Block procedures were performed under general anesthesia before the skin incision to prevent anxiety and ensure patient comfort. Thus, a preemptive effect was achieved. Following the anesthesia induction, blocks were performed under US guidance when patients were in the lateral decubitus position. After strict skin antisepsis, the needle insertion area was covered with sterile drapes. In all patients, a high-frequency 6-18 MHz linear probe (MyLab six, Esaote, Genoa, Italy) in a sterile cover was placed 2-3 cm laterally to the spinous process of the fifth thoracic (T5) vertebrae. Anatomical structures including muscles up to the transverse process, the transverse process, the paravertebral space, the internal intercostal membrane, and the pleura were visualized. A US-compatible 22-Gauge and 8-mm nerve block needle (Pajunk, SonoPlexSTIM, Germany) was used in all groups. The following procedures were performed in the study groups:

ESPB group (n:30): Following the visualization of the anatomical structures, the nerve block needle was advanced via the in-plane technique beneath the erector spinae muscles until the interfascial space was reached (**Figure 1a**). After hydrodissection with 2 ml normal saline, 20 ml 0.25% bupivacaine was injected into the area (**Figure 1b**).

TPVB group (n:30): After the visualization of the anatomical structures, the needle was advanced via the in-plane technique until reaching the paravertebral space (**Figure 1c**). A volume of 20 ml of 0.25% bupivacaine was injected into the area (**Figure 1d**).

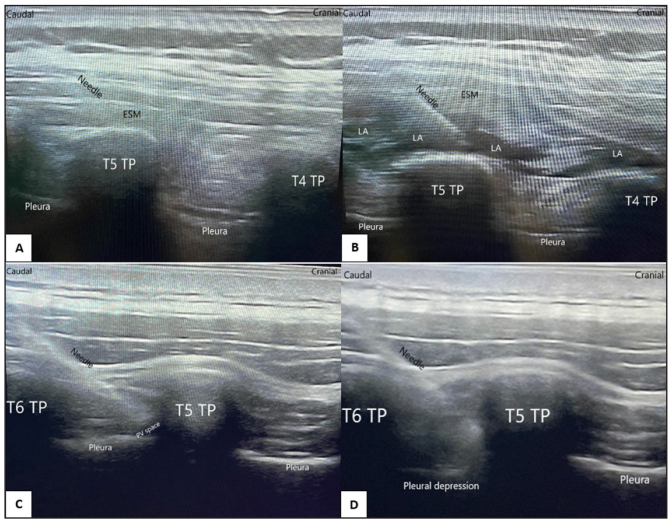

Figure 1. Anatomical view during Erector Spina Plane Block (A,B) and Thoracic Paravertebral Block (C,D). A: The view of the block needle above the transverse process and below the erector spinae muscle. B: 20 ml of 0.25% bupivacaine was administered beneath the erector spinae muscle. The local anesthetic spread caudally and cranially beneath the erector spinae muscle.C: The view of the block needle in the paravertebral space before the block. D: 20 ml of 0.25% bupivacaine was administered and pleural depression was observed. (ESM: Erector spinae muscles; LA: local anesthetic; PV space: Paravertebral space; T: Thoracic; TP: Transverse process)

Analgesia Protocol

During the skin closure, patients received intravenously administered dexketoprofen and tramadol. Metoclopramide was administered intravenously to avoid nausea and vomiting. In the postoperative surgical intensive care unit, intravenous morphine was administered via patient-controlled analgesia (PCA) pump for 24 hours. Pain intensity was evaluated using a 10- point (0: No pain and 10: Unbearable pain) visual analog scale (VAS). The PCA pump's dose delivery was limited to administer a bolus dose of 1 mg morphine and deliver a maximum dose of 12 mg morphine in total within 4 hours with lockout intervals of 15 minutes. Paracetamol 1 g every 8 hours and dexketoprofen 50 mg twice daily were administered intravenously for multimodal analgesia. As a rescue analgesic agent, 0.5 mg/kg tramadol was given to patients intravenously when a score of VAS at rest was ≥ 4. The patients were transferred to the ward in the postoperative 24th hour. Tramadol 50 mg capsules every 8 hours, paracetamol 500 mg tablets, and dexketoprofen 25 mg tablets every 12 hours were given from the second day. VAS scores at rest and while coughing were recorded in the postoperative 1st hour, 2nd hour, 4th hour, 8th hour, 12th hour, and 24th hour. The need for additional analgesics and side effects including allergic reactions, respiratory depression, sedation, urinary retention, nausea-vomiting, and itching were recorded. In two groups, patients' hemodynamic data, age, BMI, gender, diagnosis, the type of surgery, intraoperative and postoperative complications, postoperative VAS scores, and postoperative additional analgesic use were recorded. The block was applied to all patients by the same attending anesthesiologist. VAS follow-ups were performed by a pain management nurse who was blinded to the type of block applied to the patient.

The chronic pain findings of the patients were questioned by phone call. On the 30th and 90th days, the patients were called by phone and questioned whether they had burning, throbbing, numbness, electrical shock sensation, allodynia, hyperalgesia, and hypoesthesia in the surgical site. In addition, patients were asked on the 30th and 90th days whether there were pain-related limitations in activities of daily living.

Sample size and power analyses

The number of patients to participate in the study was calculated using the G*power 3.1.9.4 program, and the results of a pilot study showed that the resting 1st mean of the TPVB and ESB groups were 2.81 and 2.35, respectively, and 0.6 standard deviations (SD) in both groups. Using a bilateral t-test, 56 patients were asked to reach a power of 80% with an alpha value of 0.05 to detect differences between them, and 60 patients (30 in each group) were eligible to participate in the study. The post hoc power was calculated using G*Power© software version 3.1.9.2 (Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany). The power was calculated for the Mann Whitney U test, which was used for testing the main hypothesis (VAS rest 16th) of the present study. Depending on previous research results with two-sided (two tails) type I error 0.05 and effect size (d) factor .01, post hoc power calculated as %96.5.

Statistical Analyses

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by the Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean±SD for normal distributions, and median (Q1: first quartile - Q3: third quartile) for skewed distributions. Categorical data were described as a number of cases (%). Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t-test, Mann Whitney U tests were applied for comparisons of the not normally distributed data. Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test. It was accepted p-value < 0.05 as a significant level on all statistical analyses.

RESULTS

After ethics committee approval, the data of a total of 71 patients were analyzed. Eleven patients were excluded from the study due to conversion from VATS to open thoracotomy (**Figure 2**).

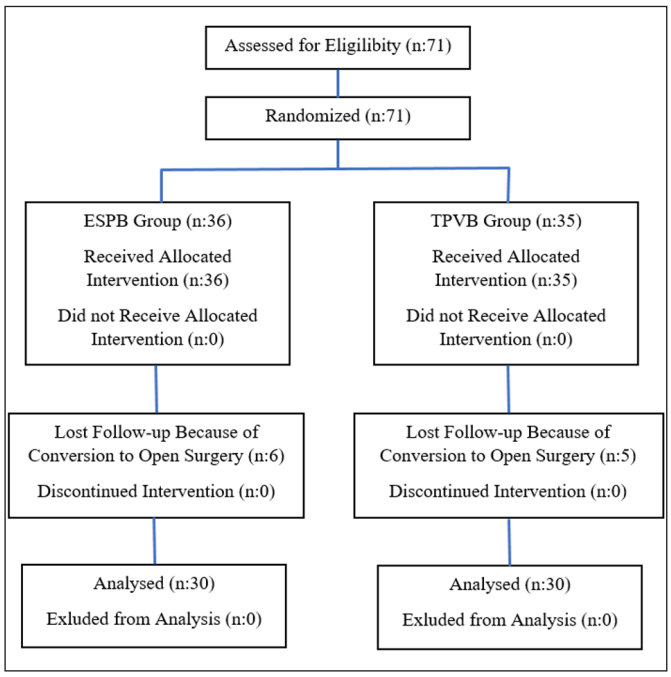

Figure 2. Flow Chart. ESPB: Erector Spinae Plane Block, TPVB: Thoracic Paravertebral Block

There was no statistically significant difference between the groups in terms of demographic characteristics, surgical features, and patient satisfaction (p>0.05) (**Table 1**).

Table 1. Demographic characteristics and surgical features of patients

	ESPB (n:30)	TPVB (n:30)	p
Age, year	57.5 (44-62)	57.5 (33-62)	0.807Φ
Gender			0.292β
Female	14 (46.7%)	10 (33.3%)	
Male	16 (53.3%)	20 (66.7%)	
BMI, kg/m²	25.78±2.77	25.59±3.24	0.929*
ASA			0.683β
1	4 (13.3%)	5 (16.7%)	
2	9 (30.0%)	12 (40.0%)	
3	17 (56.7%)	13 (43.3%)	
Surgery			0.943β
Wedge Resection	20 (66.7%)	19 (53.3%)	
Segmenthectomy	5 (16.7%)	5 (16.7%)	
Lobectomy	5 (16.7%)	6 (20.0%)	
Duration of surgery, min	150 (135-210)	175 (120-240)	0.899Φ

Continuous variables are expressed as either the mean±standard deviation (SD) or median (Q1-Q3) and categorical variables are expressed as either frequency (percentage). Student t Test *, Mann whitney u Test Φ, Chi square Test β, p=Level of Significance, p<0,05, ASA: American Society of Anesthesiologists, BMI: Body mass index, ESPB: Erector spinae plane block, TPVB: Thoracic paravertebral block

No statistically significant difference was observed between the groups in terms of mean arterial pressure, heart rate, and SpO_2 (p>0.05).

When the groups were evaluated in terms of VAS resting scores, the 1st, 2nd, 4th, 8th, and 16th-hour VAS resting results were found to be statistically significantly higher in the TPVB group than in the ESPB group (p<0.05) (**Table 2**). VAS cough scores were statistically significantly higher in the TPVB group at the 1st, 2nd, 4th, 8th, and 16th hours (p<0.05) (**Table 2**).

Table 2. Resting and coughing VAS scores of the patients during the postoperative 24 hours

	ESPB (n:30)	TPVB (n:30)	p
	Med (Q1 – Q3)	Med (Q1 – Q3)	
VAS resting			
1st hour	3 (2-4)	4 (3-5)	0.019
2nd hour	3 (2-3)	3,5 (3-5)	0.006
4th hour	2 (2-3)	3 (3-4)	0.006
8th hour	2 (2-3)	3 (2-3)	0.001
16th hour	2 (1-2)	3 (2-3)	<0.001
24th hour	2 (1-2)	2 (2-3)	0.102
VAS coughing			
1st hour	4 (3-5)	5 (4-6)	0.008
2nd hour	4 (3-5)	5 (4-6)	0.001
4th hour	3 (3-4)	4 (4-5)	0.006
8th hour	3 (3-4)	4 (3-4)	0.001
16th hour	3 (2-3)	4 (3-4)	<0.001
24th hour	3 (2-3)	3 (3-4)	0.143

*Mann whitney u test, p=Level of Significance, p<0,05, ESPB: Erector spinae plane block, TPVB: Thoracic paravertebral block, VAS: Visuel analog skala

Morphine consumption (p:0.042) and additional analgesic (p:0.037) use were found to be statistically significantly higher in the TPVB group compared to the ESPB group. As complications, only nausea and vomiting were observed with no significant difference between the groups (**Table 3**).

Table 3. Morphine consumption during postoperative 24 hours, need for additional analgesics, and complication rates

	ESPB (n:30)	TPVB (n:30)	p
Morphine consumption (mg)	13.77±8.80	18.53±8.98	0.042*
Additional analgesic use n (%)	9 (30.0%)	17 (56.7%)	0.037β
Complication (Nausea) n (%)			0.195β
No	29 (96.7%)	25 (83.3%)	
Yes	1 (3.3%)	5 (16.7%)	

Continuous variables were expressed as mean±standard deviation (SD). Categorical variables are expressed as frequency (percentage). Student t Test *, Chi square Test β, p=Level of Significance, p<0.05 ESPB: Erector spinae plane block, mg: milligram, TPVB: Thoracic paravertebral block

When the patients were evaluated in terms of the overall incidence of chronic pain and the incidence of individual chronic pain symptoms on the 30th and 90th days; no statistically significant difference was observed between the ESPB and TPVB groups (p>0.05) (**Table 4**).

Table 4. Chronic pain findings on the 30th and 90th day of the VATS

	ESPB (n:30)		TPVB (n:30)		p
	n	(%)	n	(%)	
30th day pain symptoms	18	(60.0%)	16	(53.3%)	0.602
30th day daily activity restriction	11	(36.7%)	8	(26.7%)	0.405
Burning	8	(26.7%)	6	(20.0%)	0.542
Throbbing	3	(10.0%)	7	(23.3%)	0.166
Numbness	11	(36.7%)	8	(26.7%)	0.405
Electric shock sensation	3	(10.0%)	2	(6.7%)	0.999
Allodynia	2	(6.7%)	0	(0%)	0.492
Hyperalgesia	8	(26.7%)	8	(26.7%)	0.999
Hypoestesia	6	(20.0%)	5	(16.7%)	0.739
90th day pain symptoms	5	(16.7%)	8	(26.7%)	0.347
90th day daily activity restriction	3	(10.0%)	2	(6.7%)	0.999
Burning	2	(6.7%)	5	(16.7%)	0.424
Throbbing	1	(3.3%)	3	(10.0%)	0.612
Numbness	2	(6.7%)	6	(20.0%)	0.254
Electric shock sensation	1	(3.3%)	1	(3.3%)	0.999
Allodynia	0	(0%)	0	(0%)	-
Hyperalgesia	0	(0%)	2	(6.7%)	0.492
Hypoestesia	0	(0%)	4	(13.3%)	0.112

ESPB: Erector spinae plane block, TPVB: Thoracic paravertebral block

DISCUSSION

In this randomized, prospective, single-blinded trial, the authors aimed to clarify the analgesic effects of TPVB and ESPB for acute and chronic pain in VATS procedures. The previous trials on this area included different results and inadequate data, particularly on the ESPB. In the present study, ESPB was superior to TPVB for acute postoperative pain, but the incidence of chronic pain was similar in both groups. When the side effects were evaluated, the number of patients who developed nausea and vomiting in the TPVB group was higher, although not statistically significant. This may be related to the higher dose of morphine and additional analgesic needed in the postoperative period in the TPVB group compared to ESPB.

In recent years, comparative studies of ESPB with other methods such as TPVB and intercostal block have been conducted, and various results have emerged with regard to analgesic efficacy (14,15). When evaluated in terms of its mechanism of action, clinical and cadaveric studies show that the local anesthetic distribution after ESPB is similar to that of TPVB (16,17). The possible mechanism of action of ESPB is related to the distribution of the local anesthetic solution into the paravertebral and epidural space and subsequently blocking the dorsal and ventral branches of the spinal nerve (13,18). However, when compared to TPVB, the fact that the ESPB application point is more accessible and far from the pleural area can both increase the success of the application and the complication rates may be more limited (19). The use of ESPB for analgesia in the early postoperative period after VATS seems to be advantageous compared to TPVB. In addition, ESPB's ease of application compared to TPVB and its distance from pleura and vascular structures may cause complications to suggest that it is a more appropriate block method.

In studies comparing TPVB and TEA, side effects such as hypotension, nausea/vomiting, itching, urinary retention are more limited in TPVB applications (8,10). This circumstance can be explained by the limited sympathetic and neuraxial block due to TPVB. In ESPB, the ease of application, depending on the anatomical structure, and the fact that local anesthetics do not cause central block effects, limits the side effects and complications that may occur. Although not statistically significant in our study, side effects were limited in ESPB, and nausea/vomiting was observed in only one patient.

Chronic pain causes a significant burden for patients, affects the quality of life, and is related to the risk of morbidity. Thoracic surgery is one of the procedures in which the development of chronic pain is most common. Trauma due to thoracotomy and VATS applications, especially in the intercostal nerves, is assumed to be an important factor in the development of chronic pain after thoracic surgery (5,20). Previous studies have shown the presence of chronic pain in 40% to 80% of patients after thoracotomy and in 20% to 40% after VATS (1,5,21). ESPB application was first performed by Forero et al. (12) for neuropathic pain. Although there are studies on the application of ESPB in the treatment of chronic pain (22,23), studies on the effectiveness of preoperatively applied ESPB on chronic pain are quite limited. According to our study results, patients with persistent pain symptoms on the 30th day were 53.3% in the TPVB group, while it was 60% in the ESPB group. On the 90th day, the rates were found to be 26.7% in the TPVB group and 16.7% in the ESPB group. Although there was no statistically significant difference, it was observed that the 90th-day pain rates were higher in patients who underwent TPVB. Larger series of studies on this subject will contribute to more clearly revealing the effectiveness of ESPB in preventing chronic pain.

The present study has some limitations. The study was conducted at a single center. We assessed pain scores only during the 24 hours after surgery. However, none of our patients required rescue analgesia in the ward, and the administration of routine oral analgesic medication regimens was sufficient for patients in the ward after the 24th postoperative hour. Finally, we only evaluated the incidence of chronic pain after the first and third months of surgery. Longer duration assessments may yield more descriptive results for the development of chronic pain.

CONCLUSION

ESPB was superior to TPVB in terms of acute postoperative pain control, and morphine consumption, but the incidence of chronic pain the first and third months after surgery was similar in both groups. Randomized controlled trials with larger series, using TPVB and ESPB for the prevention of postoperative pain, may be helpful in explaining the chronic pain incidence after VATS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Keçiören Training and Research Hospital Ethics Committee (Date:13.04.2021, Decision No: 2012-KAEK-15:2232).

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

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

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

REFERENCES

1. Bayman EO, Parekh KR, Keech J, et al. Preoperative patient expectations of postoperative pain are associated with moderate to severe acute pain after vats. Pain Med 2019; 20: 543-54.
2. Kwon ST, Zhao L, Reddy RM, et al. Evaluation of acute and chronic pain outcomes after robotic, video-assisted thoracoscopic surgery, or open anatomic pulmonary resection. J Thorac Cardiovasc Surg 2017; 154: 652-9.
3. Zengin M, Baldemir R, Ulger G, et al. Postoperative analgesic efficacy of thoracic paravertebral block and erector spinae plane block combination in video-assisted thoracic surgery. Cureus 2021; 13: e15614.
4. Hanley C, Wall T, Bukowska I, et al. Ultrasound-guided continuous deep serratus anterior plane block versus continuous thoracic paravertebral block for perioperative analgesia in videoscopic-assisted thoracic surgery. Eur J Pain 2020; 24: 828-38.
5. Steegers MA, Snik DM, Verhagen AF, et al. Only half of the chronic pain after thoracic surgery shows a neuropathic component. J Pain 2008; 9: 955-61.
6. Barbera C, Milito P, Punturieri M, et al. Serratus anterior plane block for hybrid transthoracic esophagectomy: a pilot study. J Pain Res 2017; 10: 73-7.
7. Komatsu T, Kino A, Inoue M, et al. Paravertebral block for video-assisted thoracoscopic surgery: analgesic effectiveness and role in fast-track surgery. Int J Surg 2014; 12: 936-9.
8. Zengin M, Alagoz A. Comparison of thoracic epidural analgesia and thoracic paravertebral block applications in the treatment of acute pain after thoracotomy in geriatric patients. Cureus 2021; 13: e18982.
9. Yeap YL, Wolfe JW, Backfish-White KM, et al. Randomized prospective study evaluating single-injection paravertebral block, paravertebral catheter, and thoracic epidural catheter for postoperative regional analgesia after video-assisted thoracoscopic surgery. J Cardiothorac Vasc Anesth 2020; 3: 1870-6.
10. Scarci M, Joshi A, Attia R. In patients undergoing thoracic surgery is paravertebral block as effective as epidural analgesia for pain management? Interact Cardiovasc Thorac Surg 2010; 10: 92-6.
11. Xu ZZ, Li X, Zhang Z, et al. Ultrasound-guided erector spinae plane block versus thoracic paravertebral block on postoperative analgesia after laparoscopic nephroureterectomy: study protocol of a randomized, double-blinded, non-inferiority design trial. Trials 2021; 22: 249.
12. Forero M, Adhikary SD, Lopez H, et al. The erector spinae plane block: a novel analgesic technique in thoracic neuropathic pain. Reg Anesth Pain Med 2016; 41: 621-7.
13. Chin KJ, El-Boghdadly K. Mechanisms of action of the erector spinae plane (ESP) block: a narrative review. Can J Anaesth 2021; 68: 387-408.
14. Turhan Ö, Sivrikoz N, Sungur Z, et al. Thoracic paravertebral block achieves better pain control than erector spinae plane block and intercostal nerve block in thoracoscopic surgery: a randomized study. J Cardiothorac Vasc Anesth 2021; 35: 2920-7.
15. Zhao H, Xin L, Feng Y. The effect of preoperative erector spinae plane vs. paravertebral blocks on patient-controlled oxycodone consumption after video-assisted thoracic surgery: A prospective randomized, blinded, non-inferiority study. J Clin Anesth 2020; 62: 109737.
16. Altiparmak B, Toker MK, Uysal Aİ, et al. Eficácia do bloqueio do plano do músculo eretor da espinha guiado por ultrassom para analgesia após colecistectomia laparoscópica: um estudo controlado randômico [Efficacy of ultrasound-guided erector spinae plane block for analgesia after laparoscopic cholecystectomy: a randomized controlled trial]. Braz J Anesthesiol 2019; 69: 561-8.
17. Yang HM, Choi YJ, Kwon HJ, et al. Comparison of injectate spread and nerve involvement between retrolaminar and erector spinae plane blocks in the thoracic region: a cadaveric study. Anaesthesia 2018; 73: 1244-50.
18. Ivanusic J, Konishi Y, Barrington MJ. A cadaveric study investigating the mechanism of action of erector spinae blockade. Reg Anesth Pain Med 2018; 43: 567-71.
19. El-Boghdadly K, Pawa A. The erector spinae plane block: plane and simple. Anaesthesia 2017; 72: 434-8.
20. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg 2009; 36: 170-80.
21. Maguire MF, Ravenscroft A, Beggs D, et al. A questionnaire study investigating the prevalence of the neuropathic component of chronic pain after thoracic surgery. Eur J Cardiothorac Surg 2006; 29: 800-5.
22. Urits I, Charipova K, Gress K, et al. Expanding role of the erector spinae plane block for postoperative and chronic pain management. Curr Pain Headache Rep 2019; 23: 71.
23. Pabón-Muñoz FE, Luna-Montúfar CA, Paredes MR. The ultrasound-guided erector spinae plane (ESP) block in chronic pain due to bone metastasis: case report. Colombian Journal of Anesthesiology 2019; 47: 128-131.

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Evaluation of proprioceptive balance results of amateur athletes following anterior cruciate ligament reconstruction: Hamstring autograft

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ABSTRACT

Aim: Anterior cruciate ligament (ACL) is one of the main ligaments which provide mechanical stability of the knee, control the anteroposterior translation and rotation movements and play a key role in neuromuscular stability. The aim of the present study is to compare the 6th month balance results on operated and non-operated sides of athletes who underwent ST/G anterior cruciate ligament reconstruction (ACL).

Material and Method: The study was evaluated as a retrospective cohort consisting of patients who underwent semitendinosus/gracilis hamstring autograft (ST/G) ACL reconstruction (n=24) technique between May 2020 and October 2021. CSMI-TecnoBody PK-252 was used to determine the 6th month post-operative static balance measurements of patients. The tests were applied to both ACLR side and contralateral healthy side.

Results: Compared to pre-operative levels, there was a significant improvement in the mean Lysholm, Tegner, and IKDC scores at the post-operative level ($p<0.05$). No significance was found between 6th month post-operative static balance results of the subjects on ACLR side and contralateral healthy side ($p>0.05$).

Conclusion: It is seen that 6 month post-operative findings of ST/G ACLR technique show similar results with the healthy contralateral side. This result is valuable in terms of balance scores showing similar results for both sides.

Keywords: Proprioception, balance, postural control, ACL reconstruction, athletes

INTRODUCTION

Anterior cruciate ligament (ACL) is one of the main ligaments which provide mechanical stability of the knee, control the anteroposterior translation and rotation movements and play a key role in neuromuscular stability because it is involved in the sensory feedback of joint movement (1-4). ACL rupture, which is one of the most common injuries in athletic population, is among the most common orthopedic surgical procedures performed in sports medicine (5). Especially in athletes, ACL injuries typically occur due to sudden deceleration, changes in direction or strong reactions to the knee (6).

Lack of neuromuscular control of the lower extremity is one of the main disorders that occur after ACL injuries (7). Especially after complete rupture of ACL; as a result of this damage, the responses to the stimuli decrease, sensitivity is affected, the ability to perceive movement is impaired, muscular atrophy occurs and the motor neurons in the muscles connected to the knee joint are inhibited (8-11). When the losses in this neuromuscular control are evaluated functionally, they can lead to loss of knee strength, balance and proprioception, and may also feel insecure (12-14). The proprioception and balance of patients after ACLR can be evaluated by many different methods. However, today, the devices that best evaluate the balance are the devices that are in the platform structure and provide us with all the detailed data for both static and dynamic balance.

After these losses in neuromuscular functions, ACL reconstruction (ACLR) is one of the surgical methods recommended by sports physicians and orthopaedists.

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Researchers have reported that appropriate rehabilitation programs after ACLR are among key factors for fixing neuromuscular losses of the lower extremity, providing dynamic and static joint stabilization and restoring functional movements to normal (11,15). Researchers have also reported that improvements in neuromuscular control also reduce re-injury rates (12). Although the exact time for full recovery and return to sports (RTS) after ACLR has not been reported, experts state that at least six months of rehabilitation and follow up are required (16,17).

Although different ACLR methods such as quadriceps tendon (QT), patellar tendon (PT) are used for both athletes and normal individuals after ACL rupture, one of the most frequently used methods is the method performed with hamstring autograft semitendinosus/gracilis (ST/G) tendons (18). The aim of the present study is to compare the 6th month balance results on operated and non-operated sides of athletes who underwent ST/G ACRL. In line with this purpose, the main hypothesis of our study is that 6th month balance results after ACLR will reveal similar findings in operated and non-operated sides in athletes. In our study, static balance findings were evaluated in terms of many parameters, not a single parameter. From this point of view, our research is one of the studies that examines the static balance parameters after ACL in detail.

MATERIAL AND METHOD

The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 31.08.2022, Decision No: SÜKAEK-2022/6/1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

The study was evaluated as a retrospective cohort consisting of patients who underwent semitendinosus/gracilis hamstring autograft (ST/G) ACL reconstruction (n=24) technique between May 2020 and October 2021. A priori test with GPower (Dusseldorf, Germany) 3.1 program was used for determining the number of participants (**Table 1**).

Table 1. Descriptive parameters

	Mean	S. D.	Min	Max
Age (year)	25.04	7.70	17	42
Height (cm)	180.13	6.87	170	195
Weight (kg)	80.58	11.18	63	105
BMI (kg/m2)	24.86	3.45	20.11	33.90
Follow up(month)	7.46	1.14	6	9
Operated knee	R 13 (54 %)	L 11 (46 %)		

S.D standard deviation; Min minimum; Max maximum; BMI body mass index; R right; L left;

Inclusion criteria of the patients were as follows: male patients between 18 and 35 years of age, patients who did not have comorbid meniscal, chondral or other ligamentous injuries, patients who had isolated ACL rupture only on one knee, patients who did not have a history of another neuromuscular or musculoskeletal system injury and contralateral knee surgery or injury. All of the patients were actively engaged in amateur sports. Lysholm, Tegner and International Knee Documentation Committee (IKDC) scores of the patients were evaluated pre-operatively and at 6th month post-operatively. All participants were referred to the same rehabilitation specialist after surgery in order to reduce variability in the recovery period.

Semitendinosus/Gracilis Autograft Method

Semitendinosus and gracilis tendon autografts taken from the same leg are used in ST/G ACLR. Gracilis and semitendinosus tendon grafts were harvested. Both tendons fold in two to form a four-strand graft. For the preparation of the femoral tunnel, the knee was moved to 90 degrees of flexion, and the guidewire inserted from the anteromedial portal was placed over the top, 2mm in front of the posterior cortex, and the femoral tunnel was opened. To create the tibial tunnel, a tibial guide was inserted into the anterior horn of the meniscus, 6 mm anterior to the posterior cruciate ligament. Suspension fixation is used to fix the graft to the femur, while interference screw fixation is used to fix it to the tibia. Fixation was done in the same way in all patients.

Procedures

Lysholm, Tegner, IKDC scores (pre and post-operative 6th month) measurements of all patients were taken. The patients visited the laboratory two times in total, including pilot measurements. At the first visit, the patients were asked to fill in the subjective surveys consisting of Lysholm, Tegner and IKDC scales and they were familiarized with the static balance measurements planned for the next visit. At the second visit (post-operative 6th month), the patients filled in Lysholm, Tegner and IKDC scales for the second time, their anthropometric measurements were taken and static balance measurements were applied.

Determination of Static Balance

CSMI-TecnoBody PK-252 was used to determine the static balance measurements of the patients. The patients were placed on the platform of the device and all tests were performed as eyes open and eyes closed for both feet, and as only eyes open for single foot. During the measurements, measurements for both feet were taken with the patient's feet on the platform of balance device, at shoulder width, with the feet on

the lines representing the x and y axes of the platform and at equal distance from the starting point, while measurements for single foot were taken with the foot placed on the middle point where the x and y axes on the platform intersected. In both double and single foot measurements, each test took 30 seconds and during the test, body position and position of the subject were monitored from the screen. At the end of the test, the results were automatically recorded in the device and then prepared for analysis. 1 minute rest period was given between the tests. Before all tests, a trial test was performed for each measurement so that the students could familiarize with the platform.

Data Analysis

SPSS 21. package program was used in the statistical analysis of the study. The results were presented as mean and standard deviation. Shapiro–Wilk test was used for normality assumption, while Levene's test was used for homogeneity assumption. Paired sample test was used to compare paired groups (operated-non-operated and pre-post). In addition, in the comparison of paired groups, effect sizes were found according to Cohen's d effect size (M2 – M1)/SDpooled). According to this formula, a d value of <0.2 was defined as weak effect size, while a d value of 0.5 was defined as moderate and a d value of >0.8 was defined as strong effect size. The statistical results were assessed within significance level of p<0.05.

RESULTS

Compared to pre-operative levels, there was a significant improvement in the mean Lysholm, Tegner, and IKDC scores at the post-operative level (p<0.05) (**Table 2, Table 3**).

Post-operative 6th month static balance values of the patients were compared in **Table 4**. According to the results, no statistical significance was found in COPX (p=.928, 95% CI= -1.81- 1.98), COPY (p=.053, 95% CI= -4.62- .04), FBSD (p=.643, 95% CI= -1.12- .71), MLSD (p= 1.00, 95% CI= -.43- .43), AFBS (p=.166, 95% CI= -5.40- .98), AMLS (p= 1.00, 95% CI= -2.09- 2.09), EA (p= .164, 95% CI= -162.29- 29.04), PE (p= .833, 95% CI= -.117.82- 95.82) and SI (p= .928, 95% CI= -2.05- 2.23) values (**Table 4)**.

Table 2. Comparison of pre-operative and post-operative levels of Lysholm, Tegner, and IKDC scores

	Pre-op	Post-op	p
	Mean±SD	Mean±SD	
Lysholm	70.83±15.81	97.16±2.48	p<0.001*
IKDC	51.42±7.65	91.96±4.95	p<0.001*
Tegner	6.43±1.35	6.00±1.58	p<0.001*

Compared to pre-operative levels, there was a significant improvement in the mean Lysholm, Tegner, and IKDC scores at the post-operative level (p < 0.05).

Table 3. Double feet static balance results of the patients

	Mean	S. D.	Min	Max
OPEN EYES				
COPX	3.63	3.24	.0	12.0
COPY	7.80	9.11	1.0	37.0
FBSD	6.50	1.72	3.0	11.0
MLSD	4.08	1.02	2.0	6.0
AFBS(mm/sec)	14.75	4.76	8.0	26.0
AMLS(mm/sec)	12.41	4.57	7.0	26.0
EA(mm2)	486.08	200.29	220.0	1096.0
P(mm)	639.67	187.70	352.0	1147.0
CLOSED EYES				
COPX	1.50	2.32	.0	10.0
COPY	6.54	10.94	.0	48.0
FBSD	5.88	3.37	2.0	15.0
MLSD	3.49	1.53	1.0	7.0
AFBS(mm/sec)	10.04	3.43	5.0	22.0
AMLS(mm/sec)	9.71	3.62	5.0	18.0
EA(mm2)	357.71	235.64	53.0	1036.0
P(mm)	474.08	149.71	261.0	873.0

S.D standard deviation; Min, minimum; Max. Maximum; COPX center of pressure X; COPY center of pressure Y; FBSD forward/ backward standard deviation; MLSD medium/lateral standard deviation; AFBS average forward/ backward speed; AMLS average medium/lateral speed; EA ellipse area; P perimeter.

Tablo 4. Operated and non-operated side comparisons of patients' eyes open static balance data

Variables	OP	NONOP	t	p	ES	95% CI	
	Mean±S.D	Mean±S.D				LB	UB
COPX	4.17±4.75	4.08±4.76	.09	.928	0.02	-1.81	1.98
COPY	3.96±4.48	6.25±5.01	-2.03	.053	0.48	-4.62	.04
FBSD	6.96±3.03	7.17±2.49	-.47	.643	0.08	-1.12	.71
MLSD	4.17±.80	4.17±1.07	.00	1.00	0.	-.43	.43
AFBS(mm/sec)	25.20±6.20	27.42±9.58	-1.43	.166	0.28	-5.40	.98
AMLS(mm/sec)	23.08±6.36	23.08±4.89	.00	1.00	0.	-2.09	2.09
EA(mm2)	509.00±253.89	575.63±264.81	-1.44	.164	0.26	-162.29	29.04
PE(mm)	1131.50±229.78	1142.50±334.54	-.21	.833	0.04	-.117.82	95.82
SI	1.21±2.14	1.13±2.13	.09	.928	0.04	-2.05	2.23

S.D, standard deviation; CI, confidence interval; LB, lower bound; UB, upper bound; OP opere; NONOP nonopere; COPX center of pressure X; COPY center of pressure Y; FBSD forward/ backward standard deviation; MLSD medium/lateral standard deviation; AFBS average forward/ backward speed; AMLS average medium/lateral speed; EA ellipse area; PE perimeter; SI stability index.

DISCUSSION

Retrospective cohort findings of our current study showed that static balance scores between ST/G ACLR performed sides and contralateral sides revealed similar findings. A finding close to statistical significance was found only in COPY parameter. Therefore, the main hypothesis of our study that 6th month balance results after ACLR technique would reveal similar findings in operated and non-operated sides in athletes was confirmed.

There are a large number of studies in literature examining balance and proprioception of subjects after different ACL autograft methods. A prospective cohort study showed that postural control and the risk of falling reached the highest scores in 4th week after ACLR, while positive recovery scores were shown after 12th week until 6th month. However, it was stated in the same study that pre-operation waiting times after ACL rupture were directly related to postural control and the risk of falling (19). Another study compared the 6th month post-operative balance scores of patients who received patellar tendon and hamstring autograft and healthy individuals and as a result found that patients who underwent ACLR showed similar balance scores with healthy individuals (20).

In a study in which balance and proprioception of patients with medial meniscal suture following ACLR and those of healthy individuals were examined, similar results were found in both groups (21). Similar to the results of the present study, it was reported in a retrospective study that patients who underwent ACLR showed reduced balanced scores in anterior-posterior movements when compared with healthy individuals (22). In the same study, similar to the results of the present study, researchers found that the balance results on ACLR side and contralateral healthy side were similar. When centre of pressure (COP) values were compared with healthy controls in other studies conducted, it was found that ACLR groups showed impaired postural control (11,23,24). This shows that, as reported in Howells et al. (22), results of both ACRL and contralateral non-operated sides which were found to be different than the control group but similar to each other show that ACRL causes bilateral balance disorders, but not unilateral balance disorders. Researchers suggest that disorders that manifest bilaterally change sensorimotor feedback from ACRL limb, affecting postural control when standing on the contralateral limb (25-27). Another group of researchers suggested that when ACL mechanoreceptors are simulated on the one side, reflex motor activities are similarly induced on both limbs (28). Such assumptions can be confirmed with the results of our study and it can be argued that feedback from ACL is important for bilateral postural control. A radiological study which was conducted on patients with completely ruptured ACL and those who did not undergo any ACLR was compared with a control group, and bilateral balance asymmetries in ACLR group was attributed to neuroplastic changes in MR results (29). Although the researches show that ACLR sides and healthy sides have similar balance scores, future studies should examine the healthy sides with different methods to determine whether they have a symptom that will affect the answers in the balance scores, and the results that can be determined exactly the similarities between the ACLR parties should be sought.

While the reasons why patients show similar balance results on both sides after ACLR have been associated with neural transmissions, researchers have reported that another reason for this change in balance elements may be caused by damage to hamstring and quadriceps muscles during ACLR (22). Hamstring muscles are known to be an important muscle group in terms of posture control and balance. Damage that occurs in hamstring mechanoreceptors after ACLR may cause mechanical traumas and incomplete functioning of the hamstring muscle group in reflexive activities by using tendons such as semitendinosus and gracilis, which are hamstring tendons, in graft selection. Researchers have shown that the hamstring muscle group responds significantly to stimuli to ACL (30,31). The use of ST/G ACLR hamstring autograft method to the subjects in our current study reveals the idea that our balance results occur due to damage in hamstring muscle. This was also reflected in our both anterior-posterior and medial-lateral results. The fact that our balance results were similar to ACLR in contralateral sides is thought to be due to the theory presented above that unilateral ACLR causes bilateral balance disorders.

When the findings of our study are evaluated in terms of RTS, it is seen that the athletes have positive findings in terms of returning to physical activity in the 6th month. Although the isokinetic strength tests or single leg hop test procedures required for RTS were not applied in our study, the researchers who applied these test procedures at the 6th month after ST/G ACLR stated that it was appropriate to return to sports (13,32,33). When evaluated with all factors, it is seen that the 6th month after ST/G ACLR is a suitable process for athletes to start sports in terms of both lower extremity strength and balance.

When all these results are evaluated, one of the main limitations of our study is revealed. In our study, healthy controls with similar fitness levels confirmed by MRI were not evaluated, only ACLR sides and contralateral healthy sides were evaluated. This has caused us not to be able to explain the similarities between contralateral sides and ACLR sides clearly. Including both patients who use different autograft methods and healthy controls in future studies will enable evaluating results more clearly.

CONCLUSION

As a result of our study, it can be seen that ST/G ACLR technique post-operative 6th month findings show similar results with healthy contralateral side. However, testing a similar experimental design with different autograft methods and healthy controls will show clearer results in terms of evaluating the effects of ST/G ACLR method on postural control and balance.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 31.08.2022, Decision No: SÜKAEK-2022/6/1).

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. Furlanetto TS, Peyré-Tartaruga LA, Pinho ASD, Bernardes EDS, Zaro MA. Proprioception, body balance, and functionality in individuals with ACL reconstruction. Acta Ortopedica Brasileira 2016; 24: 67-72.
2. Adachi N, Ochi M, Uchio Y, Iwasa J, Kuriwaka M, Ito Y. Reconstruction of the anterior cruciate ligament. J Bone Joint Surg Br 2004; 86: 515-20.
3. Anders JO, Venbrocks RA, Weinberg M. Proprioceptive skills and functional outcome after anterior cruciate ligament reconstruction with a bone-tendon-bone graft. Int Orthop 2008; 32: 627-33.
4. Fremerey RW, Lobenhoffer P, Zeichen J, Skutek M, Bosch U, Tscherne H. Proprioception after rehabilitation and reconstruction in knees with deficiency of the anterior cruciate ligament: a prospective, longitudinal study. J Bone Joint Surg Br 2000; 82: 801-6.
5. Hohmann E, Bryant A, Tetsworth K. Strength does not influence knee function in the ACL-deficient knee but is a correlate of knee function in the and ACL-reconstructed knee. Archives of orthopaedic and trauma surgery 2016; 136: 477-83.
6. Palmieri-Smith RM, Thomas AC. A neuromuscular mechanism of posttraumatic osteoarthritis associated with ACL injury. Exercise and sport sciences reviews 2009; 37: 147-53.
7. Akbari A, Ghiasi F, Mir M, Hosseinifar M. The effects of balance training on static and dynamic postural stability indices after acute ACL reconstruction. Global journal of health science 2016; 8: 68.
8. Madhavan S, Shields RK. Neuromuscular responses in individuals with anterior cruciate ligament repair. Clin Neurophysiol 2011; 122: 997-1004.
9. Machotka Z, Scarborough I, Duncan W, Kumar S, Perraton L. Anterior cruciate ligament repair with LARS (ligament advanced reinforcement system): a systematic review. Sports Med Arthrosc Rehabil Ther Technol 2010; 2: 29.
10. Shaffer SW, Harrison AL. Aging of the somatosensory system: a translational perspective. Phys Ther 2007; 87: 193-207.
11. Zouita Ben Moussa A, Zouita S, Dziri C, Ben Salah FZ. Single-leg assessment of postural stability and knee functional outcome two years after anterior cruciate ligament reconstruction. Ann Phys Rehabil Med 2009; 52: 475-84.
12. Cooper RL, Taylor NF, Feller JA. A randomised controlled trial of proprioceptive and balance training after surgical reconstruction of the anterior cruciate ligament. Research in Sports Medicine 2005; 13: 217-30.
13. Kehribar L, Yılmaz, AK, Karaduman E, et al. Post-operative results of ACL reconstruction techniques on single-leg hop tests in athletes: hamstring autograft vs. hamstring grafts fixed using adjustable cortical suspension in both the femur and tibia. Medicina 2022; 58: 435.
14. Kehribar L, Coşkun HS, Yılmaz AK, et al. Examination of ısokinetic knee strength and hamstring/quadriceps ratios in ındividuals with anterior cruciate ligament ınjury: ACL ınjured knee versus non-ınjured knee 2022; 14: 158-62.
15. Risberg MA, Holm I, Myklebust G, Engebretsen, L. Neuromuscular training versus strength training during first 6 months after anterior cruciate ligament reconstruction: a randomized clinical trial. Phys Ther 2007; 87: 737-50.
16. Zhou MW, Gu L, Chen YP, et al. Factors affecting proprioceptive recovery after anterior cruciate ligament reconstruction. Chin Med J (Engl) 2008; 121: 2224-8.
17. .Muaidi QI, Nicholson LL, Refshauge KM, Adams RD, Roe JP. Effect of anterior cruciate ligament injury and reconstruction on proprioceptive acuity of knee rotation in the transverse plane. Am J Sports Med 2009; 37: 1618-26.
18. Middleton KK, Hamilton T, Irrgang, JJ, Karlsson J, Harner CD, Fu FH. Anatomic anterior cruciate ligament (ACL) reconstruction: a global perspective. Part 1, Knee Surger Y. Sports Traumatology, Arthroscopy 2014; 22: 1467-82.
19. Gokalp O, Akkaya S, Akkaya N, et al. Preoperative and postoperative serial assessments of postural balance and fall risk in patients with arthroscopic anterior cruciate ligament reconstruction. J Back Musculoskeletal Rehab 2016; 29: 343-50.
20. Bodkin SG, Slater LV, Norte GE, Goetschius J, Hart, JM. ACL reconstructed individuals do not demonstrate deficits in postural control as measured by single-leg balance. Gait & posture 2018; 66: 296-9.
21. Parus K, Lisiński P, Huber J. Body balance control deficiencies following ACL reconstruction combined with medial meniscus suture. A preliminary report. Orthopaedics & Traumatology: Surgery & Research 2015; 101: 807-10.
22. Howells BE, Clark RA, Ardern CL, et al. The assessment of postural control and the influence of a secondary task in people with anterior cruciate ligament reconstructed knees using a Nintendo Wii Balance Board. British J Sports Med 2013; 47: 914-9.
23. Bonfim TR, Paccola CA, Barela JA. Proprioceptive and behavior impairments in individuals with anterior cruciate ligament reconstructed knees. Arch Phys Med Rehab 2003; 84: 1217–23.
24. Denti M, Randelli P, Lo Vetere D, et al. Motor control performance in the lower extremity: normals vs. anterior cruciate ligament reconstructed knees 5–8 years from the index surgery. Knee Surg Sports Traumatol Arthrosc 2000; 8: 296–300.
25. Hoffman M, Schrader J, Koceja D. An investigation of postural control in postoperative anterior cruciate ligament reconstruction patients. J Athl Train 1999; 34: 130–6.

26. Chmielewski TL, Wilk KE, Snyder-Mackler L. Changes in weight-bearing following injury or surgical reconstruction of the ACL: relationship to quadriceps strength and function. Gait Posture 2002; 16: 87–95.
27. Gauffin H, Pettersson G, Tegner Y, Tropp H. Function testing in patients with old rupture of the anterior cruciate ligament. Int J Sports Med 1990; 11: 73–7.
28. Friden T, Zatterstrom R, Lindstrand A, Moritz U. Anterior-cruciate-insufficient knees treated with physiotherapy. A 3-year follow-up study of patients with late diagnosis. Clin Orthop Relat Res 1991; 263: 190–9.
29. Kapreli E, Athanasopoulos S, Gliatis J, et al. Anterior cruciate ligament deficiency causes brain plasticity: a functional MRI study. Am J Sports Med 2009; 37: 2419–26.
30. Melnyk M, Faist M, Gothner M, Claes L, Friemert B. Changes in stretch reflex excitability are related to 'giving way' symptoms in patients with anterior cruciate ligament rüptüre. J Neurophysiol 2007; 97: 474–80.
31. Dyhre-Poulsen P, Krogsgaard MR. Muscular reflexes elicited by electrical stimulation of the anterior cruciate ligament in humans. J Appl Physiol 2000; 89: 2191–5.
32. Riesterer J, Mauch M, Paul J, Gehring D, Ritzmann R, Wenning M. Relationship between pre-and post-operative isokinetic strength after ACL reconstruction using hamstring autograft. BMC Sports Sci. Med. Rehabilitation 2020; 12: 1-10.
33. Fischer F, Fink C, Herbst E, Hoser C, Hepperger C, Blank C, Gföller P. Higher hamstring-to-quadriceps isokinetic strength ratio during the first post-operative months in patients with quadriceps tendon compared to hamstring tendon graft following ACL reconstruction. Knee Surg. Sports Traumatol. Arthrosc 2018; 26: 418-425.

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Comparison of culture-positive and culture-negative severe infectious keratitis leading to hospitalization: a tertiary referral center experience

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ABSTRACT

Aim: To compare the predisposing factors, surgical interventions, length of hospital stay (LOHS), and treatment outcomes of culture-positive (CP) versus culture-negative (CN) severe infectious keratitis (IK) resulting in hospitalization in a tertiary referral clinic.

Material and Method: We retrospectively reviewed the medical and microbiological records of 287 patients clinically diagnosed with severe keratitis over a 4-year period.

Results: Of 287 study participants, 141 (49.1%) had positive CP results. The most common ocular risk factor was a previous ocular surgery (45.6%), and keratoplasty was the first among these ocular surgeries (90.8%). *Staphylococcus epidermidis* (22.7%) was the most commonly isolated microorganism followed by fungi (17.7%). The initial and final visual acuities did not differ significantly between the CP and CN groups. Major and minor surgical interventions did not significantly differ between the groups (p=0.05). The rates of clear corneal graft in the CP group (p =0.002) were significantly higher than the rates of graft failure in the CN group (p=0.033). No significant difference was noted in the mean LOHS between groups (p=0.66). Logistic regression analyses showed that surgery during admission, *S. epidermidis* infection, and connective tissue diseases were independent risk factors for a prolonged hospital stay.

Conclusion: The initial and final visual acuities, surgical interventions, and LOHS were similar between the CP and CN groups. However, graft failure rates were significantly higher in patients with CN keratitis than in those with CP keratitis.

Keywords: Infectious keratitis, microbial culture, *Staphylococcus epidermidis*, hospitalization

INTRODUCTION

Infectious keratitis (IK) is one of the most common causes of corneal blindness in developed and developing countries (1). Although many studies have reported innovations in the etiological assessment, management, and treatment of patients with severe IK, it remains a leading cause of ocular morbidity (2-10).

Severe IK causes debilitating permanent vision loss, prolonged hospitalization, social problems, and a considerable financial burden on healthcare services (1). Additionally, IK is the main indication for corneal transplantation, with complications, such as corneal perforations and deep corneal scarring, thereby causing a sustained burden on the limited corneal donor pool. In this respect, intervention for IK is crucial to prevent visual morbidity and to support the overall healthcare system.

Although predisposing factors and clinical findings are important clues for diagnosing IK and predicting causative microorganisms, culture is accepted as the gold standard for definitive pathogen identification. Many articles have been published on culture-positive (CP) IK, in which culture isolation is defined as an indispensable test for choosing a specific drug therapy to determine antibiotic susceptibility, shorten treatment duration, and improve prognosis by identifying microbiological factors.

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However, to the best of our knowledge, only a few studies have compared CP cases with culture-negative (CN) cases of severe keratitis (11-13). Sharma et al. (11), Bhadange et al. (12) in India and Duarte et al. (13) in Brazil evaluated IK based on CP and CN results. As the populations of these countries have different characteristics, the etiologies and scenarios of IK are also quite different. Therefore, we aimed to determine the epidemiological characteristics of patients with severe IK hospitalized in Turkey and to compare predisposing factors, surgical interventions, treatment results, and length of hospital stay (LOHS) between patients with CP IK and CN IK.

MATERIAL AND METHOD

The study was carried out with the permission of Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 29.03.2021, Decision No: 2021/514/198/19). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This study had a retrospective, cross-sectional, and comparative design.

Patients and Definition of Infection

In this study, we reviewed the electronic medical records for clinical and microbiological data of 287 patients with severe IK who were hospitalized between January 2017 and December 2021. The criteria for admission were a diagnosis of severe keratitis and the need for intensive topical and systemic antimicrobial therapy, in addition to surgical treatment if necessary. The diagnosis of severe IK was based on the combination of lesion size in the longest meridian and vision loss of best-corrected visual acuity (BCVA) compared with pre-event acuity or fellow eye acuity (if acuity data were available) (14). The longest meridian was defined as central lesions >2 mm, lesions outside the central 4 mm of the cornea, lesions >4 mm, or presence of hypopyon. Exclusion criteria were a clinical diagnosis of herpetic keratitis, neurotrophic keratopathy, exposure keratopathy, and immune-mediated peripheral ulcerative keratitis. The clinical history of all the cases was considered. For all patients, medications were stopped 24 hours before sampling for culture testing. Clinical findings were followed-up regularly using slit-lamp examination, anterior segment imaging, and B-scan ultrasonography.

Microbiological Samples and Analysis

Microbiological samples for Gram staining and corneal scraping were obtained using a sterile surgical blade and cotton-tipped swab after applying topical anesthesia (0.5% proparacaine hydrochloride). The samples were examined for the presence of aerobic, anaerobic, and fungal microorganisms. Thioglycolate broth (THIO) was used to isolate the organisms from the corneal culture. The samples were incubated in THIO at 35°C for 24 h and then plated onto media (5% sheep blood agar, chocolate agar, Brucella agar, and Sabouraud dextrose agar [SDA]). For suspected amoebic corneal cases, the sample was mixed with an adequate volume of lactophenol-cotton blue stain and examined using light microscopy. Samples were considered positive for *Acanthamoeba* when the cyst walls and nucleus appeared in an intense blue color and the cytoplasm stained light blue (15). All plates were cultured in 5–7% carbon dioxide at 35°C for 72 h for bacteria or SDA for 6 weeks. The plates were evaluated daily for microorganism growth and isolate identification, and antimicrobial susceptibility tests were performed after the growth was detected (VITEK 2; Compact Systems, BioMerieux, France). Culture-positive keratitis was defined as the presence of clinical features of microbial keratitis that met at least one of the following criteria for significant growth: (1) growth of the same organism on two or more media, (2) confluent growth at the inoculation site on a solid medium, (3) growth on one medium consistent with direct microscopic findings (appropriate staining and morphology with Gram staining), and (4) growth of the same organism after repeated culture with corneal scraping material. Culture-negative keratitis was defined as a patient with clinical characteristics of microbial keratitis who did not show microbial growth on either smear or culture (16). Polymicrobial keratitis was defined as the presence of two or more types of pathogens in corneal samples of patients (9).

Data Collection and Management

For all study participants, we identified the following information from the electronic medical records: demographics, predisposing ocular and coexisting systemic factors, initial and final BCVA (with visual acuity data converted from Snellen chart values to the logarithm of the minimum angle of resolution-logMAR-), medical and surgical treatments, including both minor and major surgical interventions, duration of follow-up (days), treatment outcomes, and LOHS (days). Minor surgical interventions included amniotic membrane transplantation, intrastromal voriconazole (50 μg/mL) for fungal keratitis, and fine-needle diathermy for corneal neovascularization secondary to IK. Major surgical interventions included penetrating keratoplasty (PK) and evisceration. Data were compared between the CP and CN groups.

Before the culture results were obtained, patients were administered a combination of topical fortified antibiotics (25 mg/mL cefazolin and 14 mg/mL gentamicin, 25 mg/mL vancomycin, or 2 mg/mL linezolid and 50 mg/mL ceftazidime) once per hour. If fungal keratitis was suspected based on the clinical findings, topical fortified

10 mg/mL voriconazole or 1.5 mg/mL amphotericin B drops were administered hourly for the first 48 h, together with 1% cyclopentolate three times a day, non-preserved artificial tear drops every 2 h, and autologous serum every 3 h. If necessary, the frequency of the fortified drops was decreased every 3 h. Medical treatment was modified based on culture results and clinical response. Systemic antibacterial and/or antifungal drugs were added according to the depth, size, and clinical progression of the keratitis.

As a major surgical intervention, PK is performed for patients with corneal scarring caused by keratitis and for patients with a large (>4 mm) non-healing or perforated ulcer, usually with an urgent therapeutic or tectonic indication. The patients remained hospitalized until the infiltrate had resolved in size and depth and re-epithelialization was completed. Long hospital stay was defined as a hospital stay ≥14 days (17).

Statistical Analysis

SPSS version 25 (IBM SPSS Statistics for Windows, IBM, Armonk, NY, USA) was used for all the statistical analyses. For numerical demographic data, the standard deviation, mean, maximum, minimum, and percentage values were used. The Student's t-test was used to compare the CP and CN groups in terms of numeric demographic data. Homogeneity was evaluated using the Shapiro–Wilk test and graphical analyses. Chi-square or Fisher's tests were used to compare the CP and CN groups in terms of non-numeric demographic data. To define the independent risk factors for prolonged hospital stay, we applied logistic regression analysis to the statistically significant variables. A value of $p<0.05$ was considered statistically significant at $p<0.05$.

RESULTS

This study included 287 patients: 161 men (56.1%) and 126 women (43.9%). Of these 287 patients, the CP results were obtained in 141 (49.1%) patients, defined as the CP group and CN results were obtained in 146 (50.9%) patients, defined as the CN group. The mean age was 60.7±15.9 years in the CP group versus 59.1±17.5 years in the CN group (p=0.39). **Table 1** summarizes the patient demographic data.

The most common ocular risk factor for keratitis was ocular surgery (45.6%). No significant difference was noted between the CP and CN groups in terms of previous ocular surgery. However, a significant difference was observed between the groups in terms of history of herpetic keratitis (p<0.001) and eyelid abnormalities (p=0.009). Keratoplasty was the most common ocular surgery (90.8%) and PK was the most frequently performed keratoplasty (85.7%). Additionally, 37.4% of our patients who underwent surgery developed IK because of loose and/or broken sutures, and most of these cases were eyes with keratoplasty (p<0.001).

Table 1. Demographic data, predisposing factors, clinical characteristics and treatment outcomes.

Variables	Positive culture (Group 1) (n=141)	Negative culture (Group 2) (n=146)	p value*
Age (years), mean±SD, (range)	60.7±15.9 (21-93)	59.1±17.5 (16-91)	0.39[a]
Sex			0.46[b]
Male, n (%)	76 (47.2%)	85 (52.8%)	
Female, n (%)	65 (51.6%)	61 (48.4%)	
Length of hospital stay (days), mean±SD, (range)	15.43±11.02 (2-45)	14.81±13.03 (2-65)	0.66[a]
Visual acuity			
Initial BCVA (logMAR), mean±SD (range)	2.13±0.91 (logMAR 3-0.15)	2.32±0.91 (logMAR 3-0.15)	0.07[a]
Final BCVA (logMAR), mean±SD (range)	1.42±1.01 (logMAR 3-0.0)	1.61±1.04 (logMAR 3-0.0)	0.13[a]
Comorbidities			
Diabetes mellitus, n (%)	17 (48.6%)	18 (51.4%)	0.94[b]
Connective tissue diseases, n (%)	15 (50%)	15 (50%)	0.92[b]
Cancer, n (%)	4 (80%)	1 (20%)	0.164[c]
Atopia, n (%)	1 (20%)	4 (80%)	0.189[c]
Chronic obstructive lung disease, n (%)	6 (60%)	4 (40%)	0.48[c]
Medical treatment, n (%)	66 (49.3%)	68 (50.7%)	0.98[b]
Surgical+medical treatment, n (%)	75 (49.3%)	77 (50.7%)	0.98[b]
Major surgery, n (%)	55 (57.3%)	41 (42.7%)	0.05[b]
Minor surgery, n (%)	20 (37%)	31 (57.4%)	0.05[b]
Recurrent infection			0.101[b]
Present, n (%)	25 (61%)	16 (39%)	
Absent, n (%)	116 (47.2%)	130 (52.8%)	
Laterality			0.313[b]
Right, n (%)	65 (46.1%)	76 (53.9%)	
Left, n (%)	76 (52.1%)	70 (47.9%)	
Ocular predisposing factors			
Previous ocular surgery	69 (52.7%)	62 (47.3%)	0.271[b]
Keratoplasty	62 (47.3%)	57 (43.5%)	0.91[b]
PK	49 (37.4%)	53 (40.4%)	0.07[b]
DMEK	10 (7.6%)	4 (3.05%)	0.16[c]
DALK	3 (2.29%)	-	0.24[c]
Cataract surgery	3 (2.29%)	4 (3.05%)	0.70[c]
Cross-linking	1 (0.76%)	-	1[c]
Other	3 (2.29%)	1 (0.76%)	0.62[b]
Trauma	20 (43.5%)	26 (56.5%)	0.389[b]
Ocular surface disease	26 (55.3%)	21 (44.7%)	0.339[b]
Contact lens	11 (64.7%)	6 (35.3%)	0.185[b]
History of herpes keratitis	9 (21.4%)	33 (78.6%)	<0.001[b]
Eyelid abnormalities	25 (69.4%)	11 (30.6%)	0.009[b]
Treatment outcomes			
Healthy corneal graft	59 (41.8%)	36 (24.7%)	0.002[b]
Opaque corneal graft	26 (18.4%)	19 (13%)	0.206[b]
Vascularized leukoma	30 (21.3%)	45 (31%)	0.061[b]
Graft failure	8 (5.7%)	19 (13%)	0.033[b]
Phthisis bulbi	9 (6.4%)	10 (6.8%)	0.874[b]

* p<0.05 a Student's t-test, b Chi-squared test, c Fisher exact test
Abbreviations: BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; PK, penetrating keratoplasty; DMEK, descemet membrane endothelial keratoplasty; DALK, deep anterior lamellar keratoplasty

The difference in mean initial and final BCVA was not significant between the CP and CN groups (p=0.07 and p=0.13, respectively) (**Table 1**). Of 287 patients, 134 (46.7%) received medical therapy only, whereas 153 (53.3%) required surgical intervention. No significant intergroup differences were found in the number of patients who underwent major or minor surgery (p=0.05). Furthermore, no significant intergroup difference was found in the number of recurrent infections (p=0.101 for both groups) (**Table 1**). *Staphylococcus epidermidis* was the most commonly isolated microorganism, followed by the fungi. Fungi were the only microorganisms associated with surgical treatment (p=0.03). The isolated microorganisms are listed in **Table 2**.

Table 2. Microorganisms isolated from patients with culture-positive results

	n	%
Bacteria	100	70.9
Staphylococcus epidermidis	32	22.7
Staphylococcus aureus	11	7.8
Staphylococcus hominis	8	5.7
Pseudomonas aeruginosa	8	5.7
Haemophilus influenzae	6	4.3
Staphylococcus haemolyticus	2	1.4
Staphylococcus capitis	2	1.4
Enterobacter cloacae complex	2	1.4
Enterococcus faecium	2	1.4
Serratia spp.	2	1.4
Klebsiella spp.	2	1.4
Granulicatella spp.	1	0.7
Corynebacterium spp.	1	0.7
Fungi	25	17.7
Candida spp.	14	9.9
C. albicans	10	7.1
C. kefyr	2	1.4
C. farinata	2	1.4
Fusarium spp.	6	4.3
Aspergillus spp.	2	1.4
Penicillium	2	1.4
Geotrichum	1	0.7
Mixed (≥ 2 more bacteria or bacteria+fungi)	16	11.3
Haemophilus influenzae+Streptococcus pneumoniae	2	1.4
Staphylococcus epidermidis+Streptococcus mitis	2	1.4
Staphylococcus epidermidis+Fusarium	2	1.4
Staphylococcus epidermidis+Haemophilus influenzae	2	1.4
Haemophilus influenzae+Streptococcus pneumoniae	2	1.4
Staphylococcus epidermidis+Actinomyces	1	0.7
Staphylococcus hominis+Candida glabrata	1	0.7
Staphylococcus aureus+Haemophilus influenzae	2	1.4
Staphylococcus aureus+Enterobacter aerogenes	1	0.7
Staphylococcus warneri+*Streptococcus pneumoniae*	1	0.7
Streptococcus mitis+Streptococcus oralis	1	0.7
Enterococcus fecalis+*E. coli*	1	0.7
Enterococcus fecalis+*Pseudomonas aeruginosa*	1	0.7
Enterococcus faecium+Crytococcus neoformans	1	0.7
	141	100

We also compared treatment outcomes between the two groups. The outcomes of clear corneal grafting were better in the CP group than in the CN group (41.8% vs. 24.7%; p=0.002), whereas graft failure was more common in the CN group than in the CP group (13% vs. 5.7%; p=0.03) (Table 1). Evisceration was used as a treatment modality for 5 (1.7%) of 257 patients without connective tissue diseases versus 3 (10%) of 30 patients with connective tissue diseases (p=0.04).

The mean LOHS was 15.4±11 days (minimum, 1; maximum, 52 days) in the CP group versus 14.8±13 days (minimum 1; maximum 65 days) in the CN group (p=0.66). The overall LOHS of 128 patients (44.5%) was ≥14 days, which was defined as prolonged hospital stay. Longer hospital stay was related to the following factors: age, initial and final BCVA, ocular surface disease, surgical treatment, *S. epidermidis* infection, fungal infection, diabetes mellitus, connective tissue diseases, and atopy. According to logistic regression analyses, surgery during admission, *S. epidermidis* infection, and connective tissue diseases were independent risk factors for prolonged hospital stay. **Table 3** summarizes the logistic regression analysis of the risk factors for prolonged hospital stay.

Table 3. Logistic regression analyses

Variable	Simple linear regression	Multiple logistic regression		p value*
	p Value*	Coefficient	95% CI	
Age	0.012			
Initial BCVA (logMAR)	0.014			
Final BCVA (logMAR)	0.017			
Ocular surface disease	0.022			
Surgery during submission	<0.001	1.28	1.68-7.69	0.01
S. epidermidis	0.032	−1.31	0.1-−0.72	0.09
Fungus	0.01			
Diabetes mellitus	0.02			
Connective tissue disease	<0.001	1.72	1.34-23.42	0.018
Atopy	0.012			

* p<0.05, Abbreviations: BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution.

DISCUSSION

This study evaluated the epidemiologic features, predisposing factors, major and minor surgical interventions, LOHS, and treatment outcomes of patients with severe IK treated in our clinic, and compared these parameters between the CP and CN groups. A comparison between the CP and CN groups showed no significant differences in the initial and final visual acuity, the need for surgical intervention, or LOHS.

Our culture rates were similar to the frequencies of culture positivity reported in studies conducted in Brazil, Taiwan, and China (18,19). In our study, no significant difference was found between the CP and CN groups in terms of the initial and final visual acuity (p=0.13). Furthermore, other factors such as age and sex did not differ significantly between the groups. Similar results were reported by Bhandage et al. (12) and Yarımada et al. (20) who found that the initial and final visual acuity did not differ between the CP and CN groups.

The most common ocular risk factor for IK was previous ocular surgery in both the CP and CN groups, and thus, in the whole series (43.5%). Wong et al. (6) also reported that a previous ocular surgery was the most common predisposing factor for IK. In our study, ocular surgery was performed in almost all the patients who underwent corneal transplantation (90.8%). The identification of keratoplasty as the greatest risk factor for IK in this study may be because our center is a reference corneal transplant center, where approximately 500 keratoplasties per year are performed. Cariello et al. (18) also pointed out that previous surgery and keratoplasty, among these surgeries, were the most common predisposing factors for IK, a finding similar to this study. The rate of suture-related IK was 37.4% and most cases involved keratoplasties. This frequency is supported by other studies with suture-related IK rates between 37% and 71% (16, 21). Additionally, prolonged epithelial defects after keratoplasty, long-term corticosteroid use, and graft failure may predispose patients to IK (21,22). Therefore, it is crucial to periodically evaluate patients undergoing keratoplasty and be aware of the possibility of corneal infection. We found no significant differences in PK rates between the CP and CN groups. Although we observed that 13 of the patients diagnosed with IK after lamellar keratoplasty were in the CP group and 4 were in the CN group, this difference was not significant. Dohse et al. (22) also found no difference between the CP and CN groups in terms of IK development after penetrating and lamellar keratoplasty.

In our series, other predisposing factors following surgery were ocular surface disease (OSD) (16.37%), trauma (16.02%), and a history of herpetic keratitis (15.3%). Although the incidences of OSD and trauma were not significantly different between the groups in our study, a history of herpes was more common in the CN group. We support that necrotizing stromal keratitis due to herpes may mimic the clinical findings in CN IK (23). Bhadange et al. (12) also attributed the unresponsiveness to treatment in treatment-resistant CN keratitis to the clinical similarity between these cases and herpes-related necrotizing stromal keratitis.

In addition, eyelid abnormalities were more commonly observed in the CP group than in the CN group. Among the predisposing factors, use of contact lenses was the least common. In this study, contact lens use was mostly observed in patients with bullous keratopathy or graft failure (related to the presence of OSD). The advanced age of our series of patients may explain the association between these risk factors, and contact lens use being one of the least common risk factors.

In our study, the most frequently recovered microorganism was *S. epidermidis* (22.7%), followed by fungi. Gram-positive bacteria, including *Staphylococcus* spp. are common ocular surface commensals and are more often detected in bacterial keratitis caused by previous ocular surgery, topical steroid use, or OSD (5,21). These risk factors were also common predisposing factors in our study. This finding also supports the relationship between the more frequent observation of eyelid abnormalities in the CP group and the fact that Gram-positive bacteria were the most frequently observed microorganisms. Similar to our study, *S. epidermidis* was the most commonly isolated pathogen in studies by Wagoner et al. (21) on bacterial keratitis after PK and in large-series studies by Lin et al. (24). The second most common organism detected was fungi, among which *Candida* spp. was the most prevalent. The reason for these findings of the most commonly isolated pathogens was that most patients in our study had undergone keratoplasty. Augustin et al. (25) reported that *Candida* spp. are the most common pathogens in fungal keratitis after keratoplasty. In addition, approximately 50% of our patients with fungal keratitis required keratoplasty, and among all organisms, fungal agents were the only microorganisms for which surgical treatment was required (p=0.03). Interestingly, we did not find any cases of *Acanthamoeba* keratitis in our study.

In our study, 134 (46.7%) patients received medical therapy alone, whereas 153 (53.3%) required surgical intervention. Indeed, our study only included patients hospitalized with severe keratitis, which may explain why we performed surgical interventions more frequently than in other studies (12,13). Our polymicrobial case rate (13.4%) was higher than that reported by Bhadange (3.3%) and Duarte (no polymicrobial cases) (12,13). Many other studies have emphasized the increased need for surgery in patients with severe keratitis and polymicrobial keratitis (6,26,27). Meanwhile, no significant difference was found between the CP and CN groups in terms of the frequency of major and minor surgical interventions. This result is different from the findings of other studies that compared culture and smear results. These studies emphasized that the need for surgical intervention was higher in the CP group than in the CN group (11-13).

However, unlike these studies, because the most common predisposing factor was previous surgery and most patients had undergone keratoplasty in our series, there was a similar need for surgery in both groups, and there was no difference in the number of major and minor surgical interventions.

An intergroup comparison of the surgical treatment results in our study showed that the incidence of a healthy graft was significantly higher in the CP group than in the CN group (41.8% vs. 24.7%; p=0.002), whereas graft failure was significantly higher in the CN group than in the CP group (13.0% vs. 5.7%; p=0.033). As noted previously, Bhadange et al. (12) also reported that more patients experienced treatment failure in the CN group than in the CP group and emphasized that this failure may have been associated with herpes-related necrotizing stromal keratitis–like findings in some CN keratitis cases. In our series, the risk of graft failure may have increased because of the higher incidence of a herpes history in CN keratitis.

In our study, 128 patients (44.5%) had prolonged hospital stays. The mean LOHS did not differ between the CP and CN groups (p=0.66), and prolonged hospital stay was related to the following factors: age, initial and final BCVA, ocular surface disease, surgery during admission, *S. epidermidis* and fungal infections, diabetes mellitus, connective tissue diseases, and atopy. Subsequent logistic regression analyses revealed that surgery during admission, *S. epidermidis* infection, and connective tissue diseases were independent risk factors for longer hospital stay. The results regarding related risk factors shown in this study are in line with the findings reported in the literature, and many studies have shown that patients with IK who exhibit risk factors such as older age, diabetes mellitus, fungal keratitis, and OSD require prolonged hospital stay (6, 28-30). Similar to our results, studies in New Zealand and Taiwan have also reported that surgery during admission is associated with a longer hospital stay (6, 31). However, according to logistic regression analyses, other than surgery during admission, our results for long hospital stay differed from those in the literature, and the factors found to be related to prolonged stay, namely, *S. epidermidis* infection and connective tissue diseases, have not been previously reported. In a study from a tertiary referral center in Hungary, the authors reported that in severe microbial keratitis cases requiring enucleation and evisceration, the most commonly detected coagulase-negative staphylococci was *S. epidermidis* (32). In the same study, rheumatoid arthritis was reported to be one of the most prevalent systemic diseases (32). Among the patients included in the current study, three with severe keratitis who required evisceration had connective tissue diseases (n=8). In cases of severe keratitis, connective tissue diseases such as rheumatoid arthritis increase the possibility of complications (28,32). Therefore, an increase in complications associated with these risk factors may also lead to a prolonged hospital stay.

One of the limitations of our study was its retrospective design. Another limitation is the lack of polymerase chain reaction (PCR) analysis to exclude herpes, making clinical assessment the only method for differential diagnosis. However, our study is valuable as it is one of the largest studies in the literature comparing the CP and CN groups in severe keratitis cases, to the best of our knowledge.

CONCLUSION

This study showed that the most common predisposing factor was previous surgery, and *S. epidermidis* was the most commonly isolated microorganism. A comparison of the CP and CN groups revealed no significant difference between the groups in terms of initial and final visual acuities, needs for minor and major surgical interventions, and LOHS. However, when the two groups were compared in terms of treatment outcomes, graft failure was more frequent in the CN group. In this regard, we recommend supporting the exclusion of herpes-related keratitis via polymerase chain reaction in patients with CN keratitis..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kartal Dr. Lütfi Kırdar City Hospital Clinical Researches Ethics Committee (Date: 29.03.2021, Decision No: 2021/514/198/19).

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. Ung L, Bispo PJM, Shanbhag SS, Gilmore MS, Chodosh J. The persistent dilemma of microbial keratitis: global burden, diagnosis, and antimicrobial resistance. Surv Ophthalmol 2019; 64: 255-71.

2. Chidambaram JD, Venkatesh Prajna N, Srikanthi P, et al. Epidemiology, risk factors, and clinical outcomes in severe microbial keratitis in South India. Ophthalmic Epidemiol 2018; 25: 297-305.
3. Puig M, Weiss M, Salinas R, Johnson DA, Kheirkhah A. Etiology and risk factors for infectious keratitis in South Texas. J Ophthalmic Vis Res 2020; 15: 128-37.
4. Mohod PN, Nikose AS, Laddha PM, Shadwala Bharti. Incidence of various causes of infectious keratitis in the part of rural central India and its visual morbidity: prospective hospital-based observational study. J Clin Ophthalmol Res 2019; 7: 31.
5. Ting DSJ, Ho CS, Deshmukh R, Said DG, Dua HS. Infectious keratitis: an update on epidemiology, causative microorganisms, risk factors, and antimicrobial resistance. Eye (Lond) 2021; 35: 1084-101.
6. Wong T, Ormonde S, Gamble G, McGhee CN. Severe infective keratitis leading to hospital admission in New Zealand. Br J Ophthalmol 2003; 87: 1103-8.
7. Jin H, Parker WT, Law NW, et al. Evolving risk factors and antibiotic sensitivity patterns for microbial keratitis at a large county hospital. Br J Ophthalmol 2017; 101: 1483-87.
8. Jongkhajornpong P, Nimworaphan J, Lekhanont K, Chuckpaiwong V, Rattanasiri S. Predicting factors and prediction model for discriminating between fungal infection and bacterial infection in severe microbial keratitis. PloS One 2019; 14: e0214076.
9. Tena D, Rodríguez N, Toribio L, González-Praetorius A. Infectious keratitis: microbiological review of 297 cases. Jpn J Infect Dis 2019; 72: 121-3.
10. Egrilmez S, Yildirim-Theveny Ş. Treatment-resistant bacterial keratitis: challenges and solutions. Clin Ophthalmol 2020; 14: 287-97.
11. Sharma S, Taneja M, Gupta R, et al. Comparison of clinical and microbiological profiles in smear-positive and smear-negative cases of suspected microbial keratitis. Indian J Ophthalmol 2007; 55: 21-5.
12. Bhadange Y, Das S, Kasav MK, Sahu SK, Sharma S. Comparison of culture-negative and culture-positive microbial keratitis: cause of culture negativity, clinical features and final outcome. Br J Ophthalmol 2015; 99: 1498-502.
13. Duarte MCB, Becker GN, Muller GG, Tuon FF. Infectious keratitis in southern Brazil: a comparison culture negative and culture positive patients. Rev Bras Oftalmol 2020; 79: 46-52.
14. Stapleton F, Edwards K, Keay L, et al. Risk factors for moderate and severe microbial keratitis in daily wear contact lens users. Ophthalmology 2012; 119: 1516-21.
15. Thomas PA, Kuriakose T. Rapid detection of *Acanthamoeba* cysts in corneal scrapings by lactophenol cotton blue staining. Arch Ophthalmol 1990; 108: 168.
16. Akova YA, Onat M, Koc F, Nurozler A, Duman S. Microbial keratitis following penetrating keratoplasty. Ophthalmic Surg Lasers 1999; 30: 449-55.
17. Fransoo R, Martens P 2013. The Need to Know Team, Prior H, Burchill C, Koseva I, Bailly A, Allegro E. The 2013 RHA indicators atlas. Winnipeg, Canada: Manitoba Centre for Health Policy.
18. Cariello AJ, Passos RM, Yu MCZ, Hofling-Lima AL. Microbial keratitis at a referral center in Brazil. Int Ophthalmol 2011; 31: 197-204.
19. Hsiao CH, Sun CC, Yeh LK, et al. Shifting trends in bacterial keratitis in Taiwan: a 10-year review in a tertiary-care hospital. Cornea 2016; 35: 313-7.
20. Yarımada S, Barut Selver Ö, Palamar M, et al. Comparison of culture-positive and -negative microbial keratitis. Turk J Ophthalmol 2022; 52: 1-5.
21. Wagoner MD, Al-Swailem SA, Sutphin JE, Zimmerman MB. Bacterial keratitis after penetrating keratoplasty: incidence, microbiological profile, graft survival, and visual outcome. Ophthalmology 2007; 114: 1073-9.
22. Dohse N, Wibbelsman TD, Rapuano SB, et al. Microbial keratitis and clinical outcomes following penetrating and endothelial keratoplasty. Acta Ophthalmol 2020; 98: e895-e900.
23. Roongpoovapatr V, editor. Infectious keratitis: the great enemy. Visual impairment and blindness-what we know and what we have to know. IntechOpen, 2019.
24. Lin L, Lan W, Lou B, et al. Genus distribution of bacteria and fungi associated with keratitis in a large eye center located in Southern China. Ophthalmic Epidemiol 2017; 24: 90-6.
25. Augustin VA, Weller JM, Kruse FE, Tourtas T. Fungal interface keratitis after descemet membrane endothelial keratoplasty. Cornea 2018; 37: 1366-9.
26. Lim NCS, Lim DKA, Ray M. Polymicrobial versus monomicrobial keratitis: a retrospective comparative study. Eye Contact Lens 2013; 39: 348-54.
27. Otri AM, Fares U, Al-Aqaba MA, et al. Profile of sight-threatening infectious keratitis: a prospective study. Acta Ophthalmol 2013; 91: 643-51.
28. Koh YY, Sun CC, Hsiao CH. Epidemiology and the estimated burden of microbial keratitis on the health care system in Taiwan: a 14-year population-based study. Am J Ophthalmol 2020; 220: 152-9.
29. Toriyama K, Suzuki T, Shiraishi A. Characteristics of infectious keratitis in old and very old patients. J Ocul Pharmacol Ther 2018; 34: 565-9.
30. Khoo P, Cabrera-Aguas MP, Nguyen V, Lahra MM, Watson SL. Microbial keratitis in Sydney, Australia: risk factors, patient outcomes, and seasonal variation. Graefes Arch Clin Exp Ophthalmol 2020; 258: 1745-55.
31. Lin TY, Yeh LK, Ma DHK, et al. Risk factors and microbiological features of patients hospitalized for microbial keratitis: a 10-year study in a referral center in Taiwan. Medicine 2015; 94: e1905.
32. Tóth G, Pluzsik MT, Sándor GL, et al. Clinical review of microbial corneal ulcers resulting in enucleation and evisceration in a tertiary eye care center in Hungary. J Ophthalmol 2020; 2020: 8283131.

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The outcome of single-visit nonsurgical retreatment and patients' perception of retreatment: a retrospective cohort study with 1-year follow-up

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ABSTRACT

Aim: To evaluate the outcome of single visit nonsurgical retreatment by clinical examination and PAI (Periapical Index) and, patients' feedback regarding the nonsurgical retreatment after 1 year.

Material and Method: 115 patients who previously had nonsurgical retreatment were recalled after 1 year and after dropouts, 84 patients were examined clinically and radiographical examinations were completed pre-and postoperatively using Periapical Index. Patients were also asked if they would still choose nonsurgical retreatment for teeth with previously failed root canal treatment.

Results: The healing rate after 1 year was 88%. The tooth type did not influence the outcome (p=0.756). While the failure rate was lower in males (3.3%) than in females (16.7%), gender did not affect the outcome (p=0.088). 97.6% of patients had a positive approach to nonsurgical retreatment. There was a statistically significant relationship between treatment outcome and patients' feedback (p=0.013). There is a statistically significant positive correlation between postoperative VAS (Visual Analogue Scale) pain score and postoperative PAI score (p=0.002).

Conclusion: Single-visit nonsurgical retreatment is a viable option for teeth where certain periapical diseases such as symptomatic apical abscess are excluded. Patients, who experienced successful nonsurgical retreatment, are eager to preserve their tooth with failed primary root canal treatment when nonsurgical retreatment option is available.

Keywords: Nonsurgical retreatment, periapical index, root canal treatment

INTRODUCTION

In the case of post-treatment disease, previously root canal-treated teeth require either nonsurgical retreatment or surgical intervention (1). To retain masticatory function and to avoid further destruction of surrounding tissues and possible acute exacerbation, nonsurgical retreatment of teeth with failed post-treatment should be the first option when it is deemed as a viable option. According to the consensus report of the ESE (European Society of Endodontology), nonsurgical retreatment is indicated for teeth with inadequate root canal filling and apical periodontitis and/or symptoms (2).

During endodontic nonsurgical retreatment, clinical steps are repair of perforations, locating the previously missed root canals, shaping and disinfection of the entire canal system, and obturation respectively (1). Although cleaning, shaping, and disinfection do not differ from primary root canal treatment, locating and treating the missed portions of root canal anatomy, removing separated instruments, and bypassing the ledges can be very challenging. However, the complete healing rates of nonsurgical retreatment range from 74%-98% (3).

The outcome of root canal treatment should be monitored at least after 1 year and subsequently as required to assess the healing process. European Society of Endodontology (ESE) classifies 'favorable outcome' when pain, swelling, sinus tract, and, loss of function are absent and normal periodontal ligament space around the root is radiologically indicated (2). Progression or resolution of periapical inflammation can be evaluated by observing bone density changes from periapical radiographs. Periapical index (PAI) consists of a 5-point scale ranging from 'healthy' to 'severe periodontitis with exacerbating features'. The PAI is based on reference radiographs of teeth with verified histological diagnoses (4,5).

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It is consistently shown that patients are satisfied with root canal therapy (6,7). Studies focusing on patients' perception after root canal treatment are limited to primary root canal treatment and patient-centered outcome assessment via questionnaires can provide insight into the perception and expectations of patients about retreatment. Thus, the present study aimed to evaluate the outcome of single visit nonsurgical retreatment by clinical examination and PAI and, patients' feedback regarding the nonsurgical retreatment after 1 year. The null hypothesis was as follows: there is a statistically significant relationship between treatment outcome and patients' feedback.

MATERIAL AND METHOD

This retrospective study was carried out with the permission of Karabük University Non-interventional Clinical Research Ethics Committee (Date: 13.04.2022, Decision No: 2022/910). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

According to a power analysis (G*Power Version 3.0.10, Kiel University, Germany) (F tests, effect size f = 0.45, α error probability = 0.05, 1-β error probability = 0.85), the minimal established sample size was 77. Amongst the referred patients with post-treatment disease, 115 patients were undergone for single visit nonsurgical endodontic retreatment after clinical and radiographic examination in the Department of Endodontics. Exclusion criteria were as follows:

a. Teeth with mobility over grade 2
b. Teeth with symptomatic apical abscess
c. Teeth with root fracture
d. Teeth with a preoperative probing depth of ≥5 mm,
e. Internally or externally resorbed tooth
f. Immature teeth
g. Non-restorable teeth
h. In cases where exudate drainage present

All clinical procedures were completed by the same endodontist with 4 years of experience (Y.Ö) after recording age, gender, medical and dental history, symptoms, obtaining preoperative periapical radiographs, and informed consent form. After caries removal and access cavity preparation, previous obturation material was removed using Hedström hand files and ProTaper D1, D2, and D3 files (Dentsply Maillefer, Ballaigues, Switzerland) under rubber-dam isolation. Apical patency was established with #8-10 hand files and working length was determined with Gold Reciproc Motor (VDW GmbH, Munich, Germany). Root canal shaping was completed using Dia-X from D1 to D5 files (Diadent Group International, Europe) and 2 mL of 2.5% sodium hypochlorite was used between each file. Final irrigation was completed using 2.5% NaOCl, 17% EDTA and obturated with gutta-perchas (Dentsply Maillefer) using cold-lateral compaction technique with AH Plus root canal sealer (Dentsply Maillefer). All teeth were restored at the same visit using resin composite (Kerr, Orange, CA, USA) and postoperative periapical radiographs were obtained. Severely damaged teeth were subsequently referred for indirect coronal restorations.

All patients were recalled for follow-up after 1 year. Amongst all the cases treated (n=115), 31 patients (27%) did not attend the follow-up visits due to number of reasons including relocation, unwillingness to attend, and being unable to reach. 84 patients, since all patients, received nonsurgical retreatment only once, and therefore 84 teeth were examined clinically and radiographically by two independent examiners after obtaining informed consent. During the clinical examination, the absence/presence of spontaneous pain, sinus tract, sensitivity to percussion, and palpation were recorded. The presence of postoperative pain was evaluated with the help of a 10-point Visual Analogue Scale (VAS). Afterward, patients were asked if they would still choose retreatment over a surgical intervention when they are given multiple treatment options for another failed primary root canal treatment, and answers were also recorded.

Two independent observers who were supposed to perform radiographic examination went through a calibration procedure using PAI on another 100 digital periapical images of teeth with different periapical status (8, 9). Two calibrated examiners interpreted and scored independently the images and the scores that were agreed upon were used. A third examiner's opinion was asked in case of disagreement.

For the assessment of pre-and post-operative periapical tissues and indicators of healing; 5-point PAI was used. Periapical radiographs were obtained and saved for radiographic evaluation. The highest score of the multiple teeth was recorded. Only teeth with PAI ≤2 scores and shows no signs or symptoms were assigned as "healed", teeth scored PAI ≥3, and presence of clinical signs or symptoms were accepted as 'unhealed'.

Cohen Kappa analysis was used to evaluate the inter-observer agreement. Pearson Chi-square and Fisher's exact test were used to analyze categorical data according to treatment outcome. Mann Whitney U test was used to compare postoperative pain and PAI scores. The relationship between postoperative pain and postoperative PAI score was analyzed with Spearman's correlation. Analysis results were presented as frequency and percentage for categorical data, and median (min-max) for quantitative data. The significance level was set as $p<0.05$.

RESULTS

Interobserver kappa value was calculated as 0.86 and showed reliability in terms of periapical status assessment. Descriptive analysis of the demographic, preoperative, postoperative parameters and patients' perception of retreatment is presented in **Table 1**. The healing rate after 1 year was 88%. The highest rate of failure was observed in mandibular anterior teeth (25%). However, the tooth type did not influence the outcome (p=0.756). While the failure rate was lower in males (3.3%) than in females (16.7%), gender also did not affect the outcome (p=0.088). Amongst all the cases that were clinically examined, the rate of loss of function was 4.8%, the rate of postoperative tenderness to percussion rate was 6%, the rate of postoperative palpation rate was 2.4%, and the rate of postoperative sinus tract was 3.6%. The rate of those who had a positive approach to nonsurgical retreatment was 97.6%. While the failure rate was 9.8% amongst those who had a positive approach, all the patients with failed retreatment had a negative approach (100%) and there was a statistically significant relationship between treatment outcome and patients' feedback (p=0.013).

Table 1. Descriptive analysis of the demographic, preoperative, postoperative parameters and patients' perception of retreatment

	Healed (n=74)	Failure (n=10)	Total (n=84)	p
Tooth				0.756[2]
Maxillary anterior	14 (93.3)	1 (6.7)	15 (17.9)	
Maxillary molar	18 (85.7)	3 (14.3)	21 (25)	
Maxillary premolar	6 (100)	0 (0)	6 (7.1)	
Mandibular anterior	3 (75)	1 (25)	4 (4.8)	
Mandibular molar	25 (89.3)	3 (10.7)	28 (33.3)	
Mandibular premolar	8 (80)	2 (20)	10 (11.9)	
Gender				0.088[1]
Female	45 (83.3)	9 (16.7)	54 (64.3)	
Male	29 (96.7)	1 (3.3)	30 (35.7)	
Loss of function				**0.005**[1]
No	74 (91.3)	7 (8.6)	81 (96.4)	
Yes	0 (0)	3 (100)	3 (3.6)	
Postoperative tenderness to percussion				**<0.001**[1]
No	74 (93.7)	5 (6.3)	79 (94)	
Yes	0 (0)	5 (100)	5 (6)	
Postoperative tenderness to palpation				**0.013**[1]
No	74 (90.2)	8 (9.8)	82 (97.6)	
Yes	0 (0)	2 (100)	2 (2.4)	
Postoperative sinus track				**0.001**[1]
No	74 (91.4)	7 (8.6)	81 (96.4)	
Yes	0 (0)	3 (100)	3 (3.6)	
"Would you choose nonsurgical retreatment over surgical intervention?"				**0.013**[1]
Yes	74 (90.2)	8 (9.8)	82 (97.6)	
No	0 (0)	2 (100)	2 (2.4)	

[1]Fisher's exact test; [2]Pearson Chi Square, Statistically significant relationships are indicated with bold typeface

Comparison of postoperative pain, pre and postoperative PAI scores according to treatment outcome is presented in **Table 2**. While the median VAS pain value was 0 in healed cases, the median VAS score was 2 in failed cases, and the difference between them was statistically significant (p<0.001). The median preoperative PAI score was 4 in both healed and failed cases and there was no statistical difference between them (p=0.830). While the median value of the postoperative PAI score was 2 in healed cases, it was 3 in failed cases, and there was a statistical difference (p<0.001). There is a statistically significant positive correlation between postoperative VAS pain score and postoperative PAI score (p=0.002). It was observed that, as the pain increases, the PAI score also increases.

Table 2. Comparison of postoperative pain, pre and postoperative PAI scores according to treatment outcome

	Treatment outcome		Total	P*
	Healed	Failure		
Postoperative pain (VAS)	0 (0-0)	2 (0-6)	0 (0-6)	**<0.001**
Preoperative PAI score	4 (2-5)	4 (3-5)	4 (2-5)	0.830
Postoperative PAI score	2 (1-2)	3 (2-4)	2 (1-4)	**<0.001**

*Mann Whitney U test, Median (Min-Max)

DISCUSSION

Due to the reduced total treatment time and microleakage risk between appointments, single visit root canal treatment is favorable when it is indicated (10). Moreover, it was observed that intracanal medication with calcium hydroxide for weeks had no advantage over single visit root canal treatment in terms of periapical healing and overall treatment outcome (11). On the other hand, the influence of the number of treatment visits on nonsurgical retreatment has not been concluded due to consistent study results. While Van Nieuwenhuysen et al. (12) reported improved outcomes with multiple visits, the study of Farzaneh et al. (10) showed no significant difference. Although it was shown that active exudate drainage had no influence on the outcome of retreatment, teeth with active exudate drainage were excluded due to the potential postoperative complications after single-visit retreatment (13).

A high recall rate might lead to a less likelihood of inclusion of failed cases and therefore a biased and overestimated outcome of treatment results (14). While our recall rate was 73% and higher than some previous studies, it might be due to the fact that 1-year follow-up results in fewer dropouts than studies that have a longer follow-up period (10,15,16).

88% healing rate in the present study is close to the previous studies with a similar study design namely 85% and %90 (17,18). It could be regarded as the major

limitation of our study that 1-year follow-up might only reflect the short-term results of single-visit nonsurgical retreatment. Additionally, since the cases with a 3 PAI score were considered as "failure" despite reducing in lesion size and uncertain cases added to the failed cases, it might be speculated that a longer follow-up study could have been in a higher rate of healing. However, a recent study revealed that the outcome of root canal retreatment at 1 year is significantly correlated with survival at 4 years (19). Therefore, despite the lack of long-term follow-up results, we believe our study might contribute to the literature, considering that there are still few studies about the outcome of single-visit nonsurgical retreatment.

Results on the significance of tooth type in the outcome of nonsurgical retreatment have been inconsistent in the literature (20). In the present study, tooth type had no influence on healing rate and these results are similar to some previous studies, on the other hand opposing results identifying tooth type as an outcome predictor have been reported and lower healing rates in molars was attributed to the complexity of molar root canal anatomy (17, 21, 22). In accordance with previous studies, gender and preoperative PAI scores did not influence the outcome of nonsurgical retreatment in our study (13, 21).

Failure in root canal treatment is often associated with insufficient disinfection during the initial treatment, coronal leakage, foreign body reaction, true cyst, and vertical root fracture (23, 24). In the present study, previously formed ledges that could not be bypassed, previously separated instruments that could not be removed, and missed root canals due to the lack of use of a dental operating microscope might directly or indirectly lead to the failed cases. Unlike some of the previous studies, teeth with separated instruments were included in our study, since nonsurgical retreatment is a rational option for certain cases with separated instruments (13, 15). We believe studies including cases with previous procedural complications might reflect more realistic outcomes of nonsurgical retreatment cases.

Cone-beam computed tomography (CBCT) is proven to be helpful when it comes to identifying the missed root canals before nonsurgical retreatment (25). CBCT is also shown to detect periapical lesions significantly more precisely (26). Therefore, the lack of CBCT technology during the treatment period might have contributed to a possible underestimation of the numbers of the root canals and a likely overestimation of the healing rate.

The outcome of the nonsurgical retreatment is dramatically influenced by the operator's educational background and clinical experience (27). Due to the demanding nature of nonsurgical retreatment, it might also be argued that the healing rate and retreatment satisfaction rate could have been lower with retreatments performed by undergraduate students.

Not the quality of dental care, but how the patient perceives the dental care can be assessed, and in general, patients are satisfied with the outcome of root canal treatment (28, 29). A recent study showed that patients who underwent nonsurgical retreatment reported significant time loss from work but lower physical and psycho-social disability during the recovery phase in comparison to apical surgery (30). 97.6% of patients in the present study mentioned that they would still choose nonsurgical root canal treatment over surgical intervention. Unsurprisingly, all the patients dissatisfied with retreatment were failed cases. The null hypothesis is, therefore, accepted. However, 9.8% of the patients with failed retreatment had still a positive perception of retreatment. Cost is indicated to be the most important dissatisfaction factor with root canal treatment by patients (31). However, since all the patients were treated in a public hospital and the dental care was free of charge, we believe this fact partly contributed to the overwhelming positive perception of the patients.

CONCLUSION

Within the limitations of the present study, it could be concluded that regardless of tooth type and gender, single-visit nonsurgical retreatment is a viable option for teeth where certain periapical diseases such as symptomatic apical abscess are excluded. Patients, who experienced successful nonsurgical retreatment, are eager to preserve their tooth with failed primary root canal treatment when nonsurgical retreatment option is available.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Non-interventional Clinical Research Ethics Committee (Date: 13.04.2022, Decision No: 2022/910).

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. Roda RS, Gettleman Bradley H, Johnson Scott C. Nonsurgical retreatment. Pathways Pulp 2020: 1189-369.
2. European Society of E. Quality guidelines for endodontic treatment: consensus report of the European Society of Endodontology. Int Endod J 2006; 39: 921-30.
3. Friedman S, Mor C. The success of endodontic therapy--healing and functionality. J Calif Dent Assoc 2004; 32: 493-503.
4. Orstavik D, Kerekes K, Eriksen HM. The periapical index: a scoring system for radiographic assessment of apical periodontitis. Endod Dent Traumatol 1986; 2: 20-34.
5. Rueda-Ibarra V, Jiménez-Valdés BI, García-García HE, et al. Using the Periapical Index to evaluate the healing of periapical lesions after root canal treatment. Giornale Italiano di Endodonzia 2020; 34.
6. Gatten DL, Riedy CA, Hong SK, Johnson JD, Cohenca N. Quality of life of endodontically treated versus implant treated patients: a University-based qualitative research study. J Endod 2011; 37: 903-9.
7. Torabinejad M, Salha W, Lozada JL, Hung YL, Garbacea A. Degree of patient pain, complications, and satisfaction after root canal treatment or a single implant: a preliminary prospective investigation. J Endod 2014; 40: 1940-5.
8. Reit C. The influence of observer calibration on radiographic periapical diagnosis. Int Endod J 1987; 20: 75-81.
9. Sebring D, Kvist T, Buhlin K, Jonasson P, EndoReCo, Lund H. Calibration improves observer reliability in detecting periapical pathology on panoramic radiographs. Acta Odontol Scand 2021; 79: 554-61.
10. Farzaneh M, Abitbol S, Friedman S. Treatment outcome in endodontics: the Toronto study. Phases I and II: Orthograde retreatment. J Endod 2004; 30: 627-33.
11. Ørstavik D. Apical periodontitis: microbial infection and host responses. Essent Endod 2019: 1-10.
12. Van Nieuwenhuysen JP, Aouar M, D'Hoore W. Retreatment or radiographic monitoring in endodontics. Int Endod J 1994; 27: 75-81.
13. Serefoglu B, Micoogullari Kurt S, Kandemir Demirci G, Kaval ME, Caliskan MK. A prospective cohort study evaluating the outcome of root canal retreatment in symptomatic mandibular first molars with periapical lesions. Int Endod J 2021; 54: 2173-83.
14. Friedman S. Considerations and concepts of case selection in the management of post-treatment endodontic disease (treatment failure). Endod Topics 2002; 1: 54-78.
15. Yigit-Ozer S. Non-surgical root canal retreatment: A retrospective outcome study. Meandros Med Dent J 2020; 21: 67-72.
16. de Chevigny C, Dao TT, Basrani BR, et al. Treatment outcome in endodontics: the Toronto study--phases 3 and 4: orthograde retreatment. J Endod 2008; 34: 131-7.
17. Eyuboglu TF, Olcay K, Ozcan M. A clinical study on single-visit root canal retreatments on consecutive 173 patients: frequency of periapical complications and clinical success rate. Clin Oral Investig 2017; 21: 1761-8.
18. Pirani C, Friedman S, Gatto MR, et al. Survival and periapical health after root canal treatment with carrier-based root fillings: five-year retrospective assessment. Int Endod J 2018; 51: e178-e88.
19. Al-Nuaimi N, Ciapryna S, Chia M, Patel S, Mannocci F. A prospective study on the effect of coronal tooth structure loss on the 4-year clinical survival of root canal retreated teeth and retrospective validation of the Dental Practicality Index. Int Endod J 2020; 53: 1040-9.
20. Ng YL, Mann V, Gulabivala K. Outcome of secondary root canal treatment: a systematic review of the literature. Int Endod J 2008; 41: 1026-46.
21. Zhang M-M, Fang G-F, Chen X-T, Liang Y-H. Four-year outcome of nonsurgical root canal retreatment using cone-beam computed tomography: a prospective cohort study. J Endod 2021; 47: 382-90.
22. Pirani C, Iacono F, Gatto MR, et al. Outcome of secondary root canal treatment filled with Thermafil: a 5-year follow-up of retrospective cohort study. Clin Oral Investig 2018; 22: 1363-73.
23. Nair PN. Pathogenesis of apical periodontitis and the causes of endodontic failures. Crit Rev Oral Biol Med 2004; 15: 348-81.
24. Nair PN, Sjogren U, Figdor D, Sundqvist G. Persistent periapical radiolucencies of root-filled human teeth, failed endodontic treatments, and periapical scars. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 87: 617-27.
25. Karabucak B, Bunes A, Chehoud C, Kohli MR, Setzer F. Prevalence of apical periodontitis in endodontically treated premolars and molars with untreated canal: a cone-beam computed tomography study. J Endod 2016; 42: 538-41.
26. Davies A, Patel S, Foschi F, Andiappan M, Mitchell PJ, Mannocci F. The detection of periapical pathoses using digital periapical radiography and cone beam computed tomography in endodontically retreated teeth-part 2: a 1 year post-treatment follow-up. Int Endod J 2016; 49: 623-35.
27. Torabinejad M, Corr R, Handysides R, Shabahang S. Outcomes of nonsurgical retreatment and endodontic surgery: a systematic review. J Endod 2009; 35: 930-7.
28. Wigsten E, Al Hajj A, Jonasson P, EndoReCo, Kvist T. Patient satisfaction with root canal treatment and outcomes in the Swedish public dental health service. A prospective cohort study. Int Endod J 2021; 54: 1462-72.
29. Hamasha AA, Hatiwsh A. Quality of life and satisfaction of patients after nonsurgical primary root canal treatment provided by undergraduate students, graduate students and endodontic specialists. Int Endod J 2013; 46: 1131-9.
30. Khoo ST, Lopez V, Ode W, Yu VSH, Lui JN. Psycho-social perspectives of nonsurgical versus surgical endodontic interventions in persistent endodontic disease. Int Endod J 2022; 55: 467-79.
31. Dugas NN, Lawrence HP, Teplitsky P, Friedman S. Quality of life and satisfaction outcomes of endodontic treatment. J Endod 2002; 28: 819-27.

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The relationship between nutrition, inflammation and colchicine resistance in familial Mediterranean fever

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ABSTRACT

Aim: Familial Mediterranean fever (FMF) is an autoinflammatory and genetic disease associated with chronic inflammation. Colchicine is the gold standard treatment for FMF, although some patients respond partially. Factors such as heavy exercise, cold exposure, stress, recent infection or surgery have been associated with the occurrence of attacks. Recently, nutrition is thought to be involved in the pathogenesis of autoimmune and autoinflammatory diseases. Therefore, we aimed to investigate the relationship between nutrition, inflammation and colchicine resistance by considering the nutritional status of FMF patients.

Material and Method: The study included 59 patients and 67 healthy individuals who were matched for gender, age and body mass index (BMI). Clinical, anthropometric, and biochemical measurements were obtained. Three-days, 24-hour diet records were recorded in the nutrient database program (BeBiS software program), the amounts of macro and micronutrient contents were determined and the Diet Inflammatory Index (DII) score was calculated and compared between groups.

Results: Statistically, the diets of FMF patients were found to be higher in omega-6, carbohydrate percentage and salt content, and lower in terms of lactose, fat percentage, monounsaturated fatty acids, retinol and biotin compared to controls. There was no correlation between DII and acute phase reactants and colchicine dose.

Conclusion: The course of FMF can be affected by environmental factors, as well as its genetic background. Nutrition is a new and interesting topic in this regard and may contribute to inflammation and disease activity in FMF patients.

Keywords: Familial Mediterranean fever, inflammation, nutrition, colchicine resistance, dietary inflammatory index

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INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent fever and serosal inflammation in the peritoneum, lungs and joints. The first attack usually occurs in childhood. Attacks usually develop within a few hours and last 6-72 hours (1). FMF is common in people of Mediterranean and Middle Eastern origin and a study conducted in Turkey has shown that the prevalence of FMF is 1 in 1000. It is an autosomal recessive disease and the MEFV gene (16 p13.3) located on the short arm of chromosome 16 is responsible for the disease. FMF presents with recurrent episodes of fever and serositis that cause severe abdominal, chest, and joint pain. Although the attacks resolve spontaneously, the goals of treatment are to prevent attacks and amyloidosis, and to reduce subclinical inflammation (1).

Colchicine blocks cytokine release and microtubule polymerization, suppresses inflammation and prevents the development of amyloidosis (2). However, approximately 30-40% of patients respond partially to colchicine treatment, and 5% of these appear to be colchicine resistant (3). Although 'colchicine resistance' is not clearly defined in the literature, most commonly considered to mean more than 4 attacks in the last 6 months or more than 6 per year.

FMF is associated with chronic low-grade inflammation, and dietary components are known to influence the state of chronic low-grade inflammation. The Dietary Inflammatory Index (DII) is a literature-based scale developed to assess the potential effect of diet on inflammation. High DII score is associated with pro-inflammatory, low DII score is associated with anti-inflammatory status. The index was developed by

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reviewing a wide variety of publications and serves to assess the relationship between various dietary components and inflammatory biomarkers [tumor necrosis factor (TNF)-α, C-reactive protein (CRP), interleukin (IL)-1β, IL-4, IL-6, IL-10] (4). In the literature, high DII scores have been found to be associated with diseases accompanied by inflammation such as obesity, cardiovascular diseases, rheumatoid arthritis and cancer (5-7).

Factors such as severe stress, heavy exercise, cold exposure, recent infection and surgery and menstrual periods have been associated with the occurrence of attacks. Recently, the issue that diet has an important role in the etiopathogenesis of autoimmune diseases has been on the agenda (8,9). In addition, it has been shown that functional gastrointestinal disorders are more common in patients with FMF in recent years (9). However, studies examining the effect of nutritional habits on symptoms and treatment outcomes in FMF patients are lacking in the literature. Therefore, we aimed to investigate the relationship between nutrition, inflammation and colchicine resistance by comparing the nutritional status of FMF patients and healthy controls.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 12.01.2022, Decision No: E1-22-2320). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. We obtained written informed consent from each participant.

Study Population

This is a cross-sectional study including 59 adult FMF patients diagnosed according to Tel-Hashomer criteria and 67 healthy individuals. Those with chronic drug use other than colchicine and those with a diagnosis of chronic disease were not included in the study.

The demographic characteristics of the participants, body mass index (BMI), age at first symptom in FMF patients, age at diagnosis, clinical features of FMF, treatment content, family history of FMF, comorbidities, frequency of attacks, and sedimentation and CRP results at last visit were recorded.

We measured the participants' height using an unstretched meter while standing with their shoulders against the wall in a normal position. We measured their weight with a portable digital scale. BMI was calculated by dividing the body weight by the square of the height (kg/m²) as standard. Over at most single layer of lightweight clothing, we measured waist circumference (WC) at the umbilicus level

Attack Definition and Colchicine Resistance in FMF Patients

FMF attack was defined as fever lasting 6-72 hours (≥ 38°C) with serositis/arthritis/skin rash and elevated CRP (> 5 mg/L) and/or erythrocyte sedimentation rate (ESR) (> 20 mm/h). Colchicine resistance was defined as more than three typical attacks in last six months despite using 2 mg or more of colchicine (10). Patients who were not compliant to the colchicine treatment were excluded.

Dietary Assessment

Participants were asked to keep a record of the amount and content of the foods they consumed for three days. The days had to include two weekdays and one weekend day with normal eating habits. The participant was given both written and verbal instructions by his/her physician about recording the diet. Data regarding three-day and 24-hour diet was recorded in the licensed nutrient database program (BeBiS software program) by the same dietitian, and the average amounts of macro and micronutrient contents of the participants were determined (11).

Calculation of DII Score

DII is an index calculated on 45 nutrients and food components thought to have a potential effect of diet on the inflammatory state. In DII calculation, the Z-score values [(individual's daily food consumption/nutrient-standard global consumption amount)/food/nutrient standard deviation value] were calculated from the daily food/nutrient intakes of each individual and then converted to percentage points. To obtain a symmetrical distribution, each percentile was doubled and then "1" was subtracted. The centralized percentage values determined for each food/nutrient were multiplied by the "individual full inflammatory effect score" (4). 33 of the 45 possible foods/nutrients were used to calculate the DII from the food consumption records of the participants [energy (kcal), protein (g), total fat (g), saturated fat (g), monounsaturated fatty acids) (g), polyunsaturated fatty acids (g), n-3 fatty acid (g), n-6 fatty acid (g), cholesterol (mg), carbohydrate (g), fiber (g), caffeine (mg), vitamin a (μgr), beta carotene (μgr), vitamin d (μgr), vitamin e (mg), thiamine (mg), riboflavin (mg), niacin (mg), vitamin b6 (mg), folic acid (μgr), vitamin b12 (μg), vitamin c (mg), iron (mg), magnesium (mg), zinc (mg), selenium (μgr), green/black tea (g), onion (g), garlic (g) , pepper (g), thyme (mg), ginger (g)].

Statistical Analysis

SPSS software (version 18; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the homogeneity of the distribution of the continuous variables. Continuous variables which were not normally distributed were presented as medians (interquartile range [IQR]).

Categorical variables were analysed using χ2 test and presented as numbers. Continuous variables were compared between groups by using the Mann-Whitney U test in absence of normal distribution. Correlations between variables were analyzed using Spearman's rank correlation coefficients. A p value lower than 0.05 was considered significant. The power of the study was 87% with the current sample size using the G power program (12).

RESULTS

FMF and control groups were similar in terms of age (34 (24-43) vs. 35 (31-44), p= 0.087) and gender distribution (37 females, 22 males vs. 52 females, 15 males, p=0.067). There was no difference between the groups in terms of waist circumference, hip circumference and DII scores. Demographic characteristics and statistically different nutritional contents of all participants are presented in **Table 1**. Other than those in this table, no difference was found between the two groups in terms of all nutritional contents (vitamins, minerals, fatty acids, amino acids etc.) and it was not presented as a separate table as it would take too much space to write each.

Table 1. Demographic characteristics and statistically different nutritional contents of all participants

	FMF (n=59)	Controls (n=67)	p*
Gender	37 Female. 22 Male	52 Female. 15 Male	0.067
Age,yr	34 (24-43)	35 (31-44)	0.087
BMI,kg/m²	24.33 (20.38-29.08)	25.27 (22.67-29.47)	0.28
WC, cm	78 (84-97.5)	89 (80-99)	0.676
DII Score	0.06442 (-0.57932-0.61408)	0.07386 (-0.73262-0.71378)	0.997
Carbohydrate, %	51 (45-54)	45 (40-48)	<0.001
Carbohydrate, gr	241.3 (167.9-269.2)	189.8 (149.4-233.8)	0.051
Lactose, gr	4.6 (1.9-8.4)	6.4 (3.3-9.9)	0.05
Fat, %	36 (31-40)	39 (36-43)	<0.001
Fat, gr	68.6 (54.4-89.4)	76.3 (66.1-92)	0.072
Cholesterol, mg	209.4 (122.2-313.2)	297.1 (204.1-424.9)	0.005
Omega-6, g	19.9 (16-27)	17.9 (9.5-25.3)	0.04
Omega-6/Omega-3	15.11 (11.58-20.18)	14.90 (10.49-19.80)	0.599
Retinol, µgr	265 (190-385)	368.8 (255.4-515.3)	0.03
Biotin, µgr	31.6 (25-44)	41.2 (31.9-48.2)	0.014
Sodium,mg	4008.9 (3218.5-5043.4)	3356 (2687.1-4132)	0.02
Chloride, mg	6160.7 (4976.7-7632.2)	4802.3 (4015.5-6163.1)	0.001
Salt, gr	9.7 (7.7-12.1)	7.5 (6.3-9.6)	0.001
Iodine,µgr	161.7 (123.9-220.7)	132.2 (103.9-176.5)	0.013

BMI; body mass index; FMF, Familial Mediterranean fever; WC, waist circumference; DII, dietary inflamatuar index p* <0.05 denoted as statistically significant (in bold), Mann-Whitney U test Values are expressed as median (interquartile range)

The median age of first symptom of FMF patients was 15 (7-23), the median age of diagnosis was 23 (15-32) and the general characteristics of their diseases are given in **Table 2**.

Table 2. General disease characteristics of all FMF patients

n=59	Positive (n)	Negative (n)
Resistance	22	37
FMF symptoms		
Fever	57	2
Peritonitis	57	2
Pleuritis	12	47
Arthritis	15	44
Erysipelas	7	52
Pericarditis	0	59
Vasculitis	3	56
Amyloidosis	10	49
End stage renal disease	5	54
Family history of FMF	35	24

FMF, Familial mediterranean fever, n, number of FMF patients

In addition, a statistically significant difference was found only in terms of dietary lactose in the diet comparison made in terms of groups with and without resistance among FMF patients (5.25 (2.95-15.06) vs. 3.02 (0.89-7.24), p= 0.017), and a difference was found in terms of ESR (17 (7.75-37.5) vs. 10 (5.5-12.5), p= 0.047) and the findings are shown in **Table 3**.

Tablo 3. Dietary comparison between resistant and non-resistant FMF patients

	Resistance positive	Resistance negative	p*
Gender	11F. 11M	26F. 11M	0.12
Age,yr	39.00 (26.7-47.3)	29 (24-37)	0.95
BMI, kg/m²	24.05 (21.22-29.50)	26.23 (20.18-28.97)	0.86
WC,cm	83 (77.25-87)	92 (78-100)	0.34
ESR, mm/h	17 (7.75-37.5)	10 (5.5-12.5)	0.047
CRP, mg/L	4 (1-37.25)	5 (1-11.5)	0.886
DII Score	0.18205 (-0.59867-0.80775	0.06442 (-0.53207-0.58737)	0.88
Colchicine dose, mg	2 (1.38-2)	1.5 (1-1.5)	0.063
Lactose, gr	5.25 (2.95-15.06)	3.02 (0.89-7.24)	0.017

BMI, Body mass index; WC, waist circumference; ESR, erythrocyte sedimentation rate; CRP, C- reactive protein; DII, Dietary inflamatuar index, p* <0.05 denoted as statistically significant (in bold), Mann-Whitney U test, Values are expressed as median (interquartile range)

No correlation was found between DII and demographic characteristics in both groups, as well as acute phase reactants and colchicine dose in the FMF group, and the results are shown in **Table 4**.

Table 4. Correlation results with Dietary inflammatory index

	FMF DII score		Controls DII score	
	r	p	r	p
Age,yr	-0.099	0.465	-0.212	0.143
BMI, kg/m²	-0.131	0.550	-0.035	0.812
WC,cm	0.122	0.652	-0.153	0.316
ESR, mm/h	0.199	0.137	-	-
CRP, mg/L	0.088	0.515	-	-
Colchicine dosage,mg	0.036	0.793	-	-

BMI, body mass index; WC, waist circumference; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein, *Correlation is significant at the ≤ 0.05 level, r correlation coefficient

DISCUSSION

To the best of our knowledge, this is the first study to examine nutritional status in FMF patients to date. In our study, there was no difference between FMF patients and healthy controls in terms of DII scores. The amount of biotin in the diet of FMF patients was found to be significantly lower than in the control group. However, no difference was found between resistant and non-resistant FMF patients. Although the amount of fat was similar to the control group, the percentage of fat was found to be lower in the patient group. However, the groups were similar in terms of dietary protein and carbohydrate content, but the percentage of carbohydrate was found to be higher in the patient group. In addition, there was no difference between resistant and non-resistant FMF subgroups in terms of carbohydrate, fat and protein. While the amount of monounsaturated fatty acids in the diets of FMF patients was lower, there was no difference between the groups in terms of saturated and polyunsaturated fatty acids. However, the groups were similar in terms of omega 3, but omega-6 was statistically higher in the FMF group. Dietary lactose content and retinol content of the patient group were found to be lower than the healthy group. On the contrary, salt intake of the FMF patient group was significantly higher than the control group. Dietary iodine content was significantly higher in favour of the FMF patient group.

FMF is caused by gain-of-function mutations in the gene encoding pyrin (MEFV), a protein found in various isoforms in the cytoplasm or nucleus (13). The role of pyrin in the nucleus is not known exactly. Once activated, pyrin oligomerizes with cellular proteins and activates caspase-1 by forming a macromolecular complex called "pyrin inflammasome". Caspase-1 causes the release of proinflammatory IL-1β and IL-18, resulting in pyroptosis, the inflammatory death of cells. IL-1β contributes to the inflammatory burst by stimulating the expression of genes involved in the IL-1 pathway. Pyrin expression can be upregulated by lipopolysaccharides (LPS) and cytokines such as interferon (IFN)-γ, TNF-α, IL-4 and IL-10. Pyrin is expressed in innate cells, including monocytes, granulocytes, dendritic cells, synovial and serosal fibroblasts. Over activation of the pyrin inflammasome and consequent inflammation triggers the febrile inflammatory episodes, typical of FMF (14).

Diet plays an important role in chronic inflammation and the DII is a scale developed to assess this condition. For example, an inverse relationship between fruit and vegetable consumption and inflammatory markers such as CRP, IL-6 and TNF-α has been shown in the literature (15). In our study, DII scores of FMF and control groups were similar. Despite the high number of patients with colchicine resistance in our study, there was no correlation between ESR and CRP and DII in the FMF group. This result may have been due to our sample size or the predominance of genetic features in the etiopathogenesis.

Biotin is a B-complex vitamin that acts as the main coenzyme for five carboxylases in the body: Coenzyme for pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase 1 and 2. Since these enzymes are involved in various metabolic pathways such as gluconeogenesis, amino acid metabolism and fatty acid synthesis, inflammatory and immunological disorders may accompany biotin deficiency (16). Although the mechanisms of this situation have not been clarified yet, one of the mechanisms that may be related to FMF may be the effect of biotin levels on transcriptional factors such as Nuclear Factor kappa B (NF-κB). It has been shown in the literature that the nuclear abundance and transcriptional activity of NF-κB are significantly higher in biotin-deficient cells than in biotin-supplemented cells (17). In addition, it has been shown that IL-1β and TNF-α increase in biotin deficiency. In the study of Kuroishi et al. (18), TNF-α production in biotin-deficient macrophages was found to be significantly higher than in biotin-sufficient macrophages, and this was down-regulated by biotin supplementation. Wiedmann et al. (19), on the other hand, found that IL-1β, IFN-γ and Ig μ chain in gene expression analysis in concanavalin A stimulated peripheral blood mononuclear cells isolated from healthy adults before or after biotin supplementation for 3 weeks, showed that it was up-regulated after biotin supplementation. Although these seem to be conflicting, the experimental conditions were different. Also it is logical that biotin supplementation would up-regulate IFN-γ. Biotin plays an important role in the maturation and responsiveness of immune cells, the function of natural killer (NK) lymphocytes, and the formation of cytotoxic T lymphocytes. T cell and B cell immunity may be impaired due to biotin deficiency.

Current evidence indicates that biotin has a vital role in chromatin structure and gene expression. Biotin maintains genome stability by binding to histones and playing a role in transcriptional repression of genes (16). In our study, the amount of biotin in the diets of FMF patients was found to be significantly lower than in the control group. However, no difference was found between resistant and non-resistant FMF patients. Based on all these results, we hypothesized that biotin supplementation in order to reduce inflammation in FMF patients may contribute to the clinical improvement.

Recent studies have provided advances in demonstrating the relationship between nutrition/metabolic regulation and immunological/inflammatory functions (20). Immunological responses such as lymphocyte proliferation

and cytokine production are metabolically costly, and nutritional and metabolic conditions are expected to affect immunological function. In 1961, Mellinkoff et al. (21) suggested that a low-fat diet reduces the incidence of fever episodes in patients with FMF and that there is a close relationship between dietary imbalances and exacerbations. In a study a year later, Sohar et al. (22) suggested that a low-fat diet had no effect on attack frequency in FMF patients who had not previously taken colchicine. No other studies have been conducted in subsequent years to elucidate the effect of diet on FMF, and the role of diet in this condition has been underestimated. Although it is accepted that carbohydrates have inflammatory effects in relation to the glycemic index (GI) and glycemic load (GL) of foods, this issue is still controversial in the literature. Hu et al. (23) showed a positive relationship between dietary GI and oxidative stress, and another study showed that high GI carbohydrates increased NF-κB activation (24). It has also been reported that relatively high consumption of both soluble and insoluble fibre is inversely related to IL-6 and TNF-α, but not to CRP levels. Presumably, the inflammatory response may differ depending on the type of carbohydrate (25). In our study, although the amount of fat in the diet of FMF patients was similar to the control group, their fat percentage was found to be lower. Although the amount of dietary protein and carbohydrate was similar between the groups, the percentage of carbohydrates was found to be higher in the patient group. In addition, in the FMF subgroups, no difference was found in terms of carbohydrate, fat and protein. However, since the GI and GL of carbohydrates were not calculated in our study, it is not possible to reach an absolute conclusion on this subject for now, and further studies will be beneficial.

Monounsaturated fatty acids (MUFA), moderately saturated fatty acids (SFA) and polyunsaturated fatty acids (PUFA) have anti-inflammatory activity and have protective effects on the immune-mediated inflammatory response (26). In our study, while the amount of monounsaturated fatty acids was found to be lower in the diets of FMF patients, which may be related to this mechanism, there was no difference between the groups in terms of saturated and polyunsaturated fatty acids.

PUFAs are omega-3 and omega-6 fatty acids. Long-chain omega-3 fatty acids (LCn3) include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish, and alpha-linolenic acid (ALA) found in some vegetable oils (including hazelnuts and peanuts). Many vegetable oils contain omega-6 fats, especially linoleic acid (LA). Omega-6 (LA) has been associated with proinflammatory effects and its derivative arachidonic acid (AA) is a precursor for key proinflammatory mediators, while LCn3 reduces various physiological aspects of inflammation and production of prostaglandin and leukotrienes from omega-6 (27). In our study, although the groups were similar in terms of omega 3, omega-6 was found to be statistically higher in the FMF group. This suggests that adding omega 3 to the diet may be beneficial in reducing inflammation.

After the recognition of inflammation as an important research area in nutritional sciences, dairy products have become a food type that has attracted attention to work in this context. Milk is a natural food that contributes to prebiotics and probiotics acting on immunity, inflammatory processes and microflora. Studies on the effect of dairy products on inflammatory processes have reported conflicting results such as beneficial, ineffective and harmful (28). In a study of various patient groups, the proinflammatory effect of dairy products was determined in people with milk allergies (27). However, a recent systematic review concluded that dairy consumption had no adverse effects on biomarkers of inflammation in overweight and obese subjects (29). Bioactive peptides and glycans derived from bacterial fermentation of milk can interact with both the microbiota and immune cells, contributing to its anti-inflammatory activity (30). In our study, the amount of lactose in the diet of the FMF group was found to be lower than that of the control group. This may be due to either the contribution of lactose deficiency to inflammation or the high prevalence of lactose intolerance in Turkish society, and that patients reduce their milk intake to avoid abdominal discomfort.

Vitamin A is available in forms such as retinal, retinol, and retinoic acids and is an essential micronutrient. Vitamin A in dietary is absorbed from retinoids as retinol or as pro-vitamin A carotenoids, which are converted to retinol in the enterocyte. Vitamin A is an important component of immunity as well as having many functions such as embryological development, cellular differentiation, growth, vision and reproduction. Vitamin A regenerates the mucosal barriers, contributes to the innate immune function by supporting neutrophils, macrophages and NK cells, and its deficiency can impair both innate and adaptive immune functions (31). In our study, dietary retinol levels of FMF patients were found to be lower than the healthy group. Studies are needed to investigate the contribution of vitamin A supplementation to disease activity in these patients.

Salt is an important component of the diet, polarizing adaptive and innate immune cells towards the proinflammatory side and causing partial damage to target organs. Dendritic cells activated by excess sodium increase the production of IL-1β and the T cell cytokines IL-17A and IFN-γ (32). Macrophages are classified into proinflammatory M1 and anti-inflammatory M^2 phenotypes, which play important roles in mediating T helper (Th) 2 immunity, suppressing effector T cell

function, and wound healing. However, NaCl causes blunting of activation of M² macrophages (33). Salt induces proinflammatory cells such as Th 17 and restricts the reparative effects of M1 macrophages and regulatory T cells and M² macrophages. Also critical for the formation of a Th 17 response, the inflammasome can induce widespread inflammatory responses after exposure to a high-salt environment. Studies have shown that excessive salt intake disrupts the balance between immunosuppressive and inflammatory effects and represents an environmental risk factor for the development of autoimmune diseases, arterial hypertension and perhaps other diseases whose associations will emerge in the future (34). In our study, surprisingly, salt intake in the diet of the FMF group was significantly higher than that of the control group. In the future, perhaps, interventional studies will show that salt is a factor that may contribute to increased inflammation in these patients.

Innate immunity related alterations are prominent in the pathogenesis in FMF, whereas adaptive immunity changes are prominent in autoimmune thyroid disease, which is thought to be related to iodine. However, in our study, the dietary iodine content of FMF patients was significantly higher than the healthy group. In addition, there was no difference in terms of iodine between the FMF patients with and without resistance. However, since thyroid function tests (TFT) were not recorded in our study, the effect of the current iodine level on TFT could not be examined.

The limitations of our study are as follows; relatively small sample size, not controlling factors such as retinol, biotin, fatty acids in the serum, not questioning lactose intolerance, not recording thyroid function test results, and not specifying the types of foods. The strength of our study is that it is the first study in the field of nutrition in FMF patients, in which all components of the diet were examined, and the number of patients with colchicine resistance was high.

CONCLUSION

FMF disease can be affected by environmental factors as well as genetic background. Nutrition is a new and interesting topic in this regard. In our study, the diets of FMF patients were found to be higher in omega-6, carbohydrate percentage and salt content, and lower in lactose, fat percentage, monounsaturated fatty acids, retinol and biotin compared to the control group. Our current data suggests that diet may partially contribute to inflammation and disease activity in FMF and future large-scale nutritional intervention studies may further elucidate this issue.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 12.01.2022, Decision No: E1-22-2320).

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. Ozdogan H, Ugurlu S. Familial Mediterranean Fever. Presse Med 2019; 48: 61–76.
2. Erer B, Demirkaya E, Ozen S, Kallinich T. What is the best acute phase reactant for familial Mediterranean fever follow-up and its role in the prediction of complications? A systematic review. Rheumatol Int 2016; 36: 483–7.
3. Ben-Chetrit E, Aamar S. About colchicine compliance, resistance and virulence. Clin Exp Rheumatol 2009; 27: 1–3.
4. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr 2014; 17: 1689–96.
5. Garcia-Arellano A, Ramallal R, Ruiz-Canela M, et al. Predimed Investigators. Dietary Inflammatory Index and Incidence of Cardiovascular Disease in the PREDIMED Study. Nutrients 2015; 7: 4124–38.
6. Fowler ME, Akinyemiju TF. Meta-analysis of the association between dietary inflammatory index (DII) and cancer outcomes. Int J Cancer 2017; 141: 2215–27.
7. Matsumoto Y, Shivappa N, Sugioka Y, et al. Change in dietary inflammatory index score is associated with control of long-term rheumatoid arthritis disease activity in a Japanese cohort: the TOMORROW study. Arthritis Res Ther 2021; 23: 105.
8. Rambod M, Nazarinia M, Raieskarimian F. The impact of dietary habits on the pathogenesis of rheumatoid arthritis: a case-control study. Clin Rheumatol 2018; 37: 2643–48.
9. Scrivo R, Perricone C, Altobelli A, et al. Dietary Habits Bursting into the Complex Pathogenesis of Autoimmune Diseases: The Emerging Role of Salt from Experimental and Clinical Studies. Nutrients 2019; 11: 1013.
10. Korkmaz C, Ozdogan H, Kasapçopur O, Yazici H. Acute phase response in familial Mediterranean fever. Ann Rheum Dis 2002; 61: 79–81.
11. Ebispro for Windows, Stuttgart, Germany; Turkish Version (BeBiS 8.2) (2019) Pasifik Elektirik Elektronik Ltd. Şti. (www.bebis.com.tr); Istanbul
12. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007; 39:175-91.
13. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997; 17: 25–31.

14. Liston A, Masters SL. Homeostasis-altering molecular processes as mechanisms of inflammasome activation. Nat Rev Immunol 2017; 17: 208–14.
15. Hermsdorff HH, Zulet MA, Puchau B, Martínez JA. Fruit and vegetable consumption and proinflammatory gene expression from peripheral blood mononuclear cells in young adults: a translational study. Nutr Metab 2010; 7: 42.
16. Agrawal S, Agrawal A, Said HM. Biotin deficiency enhances the inflammatory response of human dendritic cells. Am J Physiol Cell Physiol 2016; 311: 386–91.
17. Rodriguez-Melendez R, Schwab LD, Zempleni J. Jurkat cells respond to biotin deficiency with increased nuclear translocation of NF-kappaB, mediating cell survival. International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Int J Vitam Nutr Res 2004; 74: 209–16.
18. Kuroishi T, Endo Y, Muramoto K, Sugawara S. Biotin deficiency up-regulates TNF-alpha production in murine macrophages. J Leukoc Biol 2008; 83: 912–20.
19. Wiedmann S, Eudy JD, Zempleni J. Biotin supplementation increases expression of genes encoding interferon-gamma, interleukin-1beta, and 3-methylcrotonyl-CoA carboxylase, and decreases expression of the gene encoding interleukin-4 in human peripheral blood mononuclear cells. J Nutr 2003; 133: 716–19.
20. Hotamisligil GS, Erbay E. Nutrient sensing and inflammation in metabolic diseases. Nat Rev Immunol 2008; 8: 923–34.
21. Mellinkoff SM, Schwabe AD, Lawrence JS. A Dietary Treatment for Familial Mediterranean Fever. Arch Intern Med 1961; 108: 80-5.
22. Sohar E, Gafni J, Chaimow M, Prass M, Heller H. Low-Fat Diet in Familial Mediterranean Fever. A Therapeutic Trial. Arch Intern Med 1962; 110: 150-4.
23. Hu Y, Block G, Norkus EP, Morrow JD, Dietrich M, Hudes M. Relations of glycemic index and glycemic load with plasma oxidative stress markers. Am J Clin Nutr 2006; 84: 70–6.
24. Dickinson S, Hancock DP, Petocz P, Ceriello A, Brand-Miller J. High-glycemic index carbohydrate increases nuclear factor-kappaB activation in mononuclear cells of young, lean healthy subjects. Am J Clin Nutr 2008; 87: 1188–93.
25. Ma Y, Hébert JR, Li W, et al. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. Nutrition 2008; 24: 941–9.
26. Casas R, Estruch R, Sacanella E. The Protective Effects of Extra Virgin Olive Oil on Immune-mediated Inflammatory Responses. Endocr Metab Immune Disord Drug Targets 2018; 18: 23–35.
27. Innes JK, Calder PC. Omega-6 fatty acids and inflammation. Prostaglandins Leukot Essent Fatty Acids 2018; 132: 41–8.
28. Bordoni A, Danesi F, Dardevet D, et al. Dairy products and inflammation: A review of the clinical evidence. Crit Rev Food Sci Nutr 2017; 57: 2497–2525.
29. Labonté MÈ, Couture P, Richard C, Desroches S, Lamarche B. Impact of dairy products on biomarkers of inflammation: a systematic review of randomized controlled nutritional intervention studies in overweight and obese adults. Am J Clin Nutr 2013; 97: 706–17.
30. Tsai YT, Cheng PC, Pan T M. The immunomodulatory effects of lactic acid bacteria for improving immune functions and benefits. Appl Microbiol Biotechnol 2012; 96: 853–62.
31. Tanumihardjo SA, Russell RM, Stephensen CB, et al. Biomarkers of Nutrition for Development (BOND)-Vitamin A Review. J Nutr 2016; 146: 1816S–48S.
32. Barbaro NR, Foss JD, Kryshtal DO, et al. Dendritic Cell Amiloride-Sensitive Channels Mediate Sodium-Induced Inflammation and Hypertension. Cell Rep 2017; 21: 1009–20.
33. Binger KJ, Gebhardt M, Heinig M, et al. High salt reduces the activation of IL-4- and IL-13-stimulated macrophages. J Clin Invest 2015; 125: 4223–38.
34. Ip WK, Medzhitov R. Macrophages monitor tissue osmolarity and induce inflammatory response through NLRP3 and NLRC4 inflammasome activation. Nat Commun 2015; 6: 6931.

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Comparison between closed reduction plaster casting and percutaneous Kirschner wire pinning in the management of distal radius fractures in patients aged 65 years and older

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ABSTRACT

Aim: Closed reduction plaster casting (CRPC) and percutaneous pinning (CRPP) remain an important treatment modalities for extra-articular distal radius fractures especially in elderly patients. These two treatment methods have advantages and disadvantages compared to each other. The ideal treatment of extra-articular distal radius fractures is still debatable. We aimed to retrospectively evaluate the clinical and radiological results after CRPC and CRPP for the treatment of distal radius fractures in the patient population over 65 years of age.

Material and Method: Between 1 January 2015 and 1 January 2019, patients older than 65 years of age who presented with extra-articular noncomminuted distal radius fractures were retrospectively evaluated. 95 patients diagnosed with distal radius fracture were separated into 2 groups, who were administered the following: CRPC (n:51), CRPP (n:44). We compared the characteristics of the patients, the mechanisms of injury, fracture types and treatment methods, pre-reduction and post-reduction radiological parameters and clinical functions for the two groups. Volar tilt, radial inclination, ulnar variance, and radial length were compared. Clinical results were also compared.

Results: The mean follow-up period was 19.8 months (range, 12-29 months; SD=11.0) in the CRPC group and 18.6 months (range, 12-26 months; SD=10.9) in the CRPP group. Mean range of motion and grip strength were maintained in both treatment groups at one-year follow-up. There was no statistically significant difference between the groups ($p>0.05$). There was no statistically significant difference between the groups in terms of the scores evaluating the daily activity, pain and mental status of the patients after the treatment ($p>0.05$). There are no statistically significant differences between fixation with CRPC and CRPP in terms of clinical and radiological results ($p>0.05$).

Conclusion: Closed reduction plaster casting and closed reduction percutaneous pinning are equally effective in the treatment of extra-articular distal radius fractures in the elderly.

Keywords: Distal, radius fracture, closed fracture reduction, fracture fixation, Kirschner wires

INTRODUCTION

Fractures of the distal radius are commonly encountered in orthopaedic practice with increasing numbers of low energy fractures in the elderly (1). Due to a more active and expanding elderly population in recent years, the incidence of distal radius fractures has been gradually increasing (2). Distal radius fractures are caused by two very different injury mechanisms. Firstly, porotic fractures in elderly patients and the other is traumatic fractures in young patients. Differences in this injury mechanism and related groups may explain the reason for conflicting statements in publications. Today's information suggests that distal radius fractures in elderly patients represent an insufficiency fracture associated with all risk factors for osteoporosis (3).

Various types of fractures of the distal radius can be treated with different treatment methods. Due to the lack of scientific evidence, specific treatment methods for fracture types cannot be recommended (4). Treatment principles,

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strategies and clinical outcomes for distal radius fractures differ, especially in the elderly patient population. The critical evaluation of the initial radiological imaging is important to recognize the features and stability of the fracture. The fracture pattern, injury mechanism, soft-tissue injury, patient characteristics, and surgeon preference are generally taken into consideration when choosing the most appropriate modality (5). Treatment of distal radius fractures has undergone a very unusual development over the past two decades. In addition to traditional plaster cast treatment, bridge external fixator, dorsal support plate and volar locked plate treatment options are developed. Whichever treatment option we choose, the goal of treatment should be to reduce pain and restore function.

In his original article Abraham Colles noted that "In all its movements in a distant period, it will have the perfect freedom again and will be completely free of pain." (6). Current information confirms that patients over 65 years of age with extra-articular unstable fractures may have satisfactory functional results with the closed treatment method compared to younger patients. Older patients can tolerate more radiographic alignment defects; It was found that the results between the surgical and nonsurgical treatments in patients aged 65 and over were equal (7). Closed reduction with percutaneous pin fixation and/or external fixation have historically been the most common treatment methods for unstable injuries (8, 9).

Closed reduction plaster casting (CRPC) and closed reduction percutaneous pinning (CRPP) remain an important treatment modalities for distal radius fractures especially in elderly patients. These two treatment methods have advantages and disadvantages compared to each other. Most studies define the elderly as patients between the ages of 50 and 75 (7, 10, 11). In this study, patients aged 65 and over were defined as elderly. We aimed to retrospectively evaluate the clinical and radiological results after CRPC and CRPP for the treatment of distal radius fractures in the patient population over 65 years of age.

MATERIAL AND METHOD

Study Design

This retrospective, multicenter study was carried out with the permission of Ondokuz Mayıs University Clinical Research Ethics Committee (Date: 07.02.2019, Decision No: 2019/114). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included a total of 95 patients older than 65 years of age who presented at the Department of Orthopedics and Traumatology at Ondokuz Mayıs and Amasya Universites Faculty of Medicine between 1 January 2015 and 1 January 2019. We used billing records to identify all skeletally mature patients with extra-articular distal radius fractures treated with CRPC and CRPP at two Level I trauma centers. All the details of this clinical study were explained to the patients, and all participated in the study voluntarily, providing written informed consent.

Sample and Sampling

A total of 95 patients older than 65 years of age who diagnosed with distal radius fracture were separated into 2 groups, who were administered the following: CRPC (n:51), CRPP (n:44). We compared the characteristics of the patients, the mechanisms of injury, fracture types and treatment methods, pre-reduction and post-reduction radiological parameters and clinical functions for the two groups. Volar tilt, radial inclination, ulnar variance, and radial length were compared. Clinical results were also compared.

Patients were informed about the potential risks and benefits of both CRPC and CRPP, and the decision was made by the patient. Eight patients had excessive soft tissue swelling on admission, and they were treated with CRPP. Nine patients with increased risk for surgery due to co-existing medical conditions were treated with CRPC. There were 51 patients in the CRPC group and 44 in the CRPP group.

Patients over 65 years of age who presented with unstable, dorsally displaced, no-articular stepping, extra-articular fracture of the distal radial metaphysis (AO-A3) (12) or Frykman types I and II (13) distal radius fractures were included in this study. The fractures were classified according to the AO classification system. There were no distal radioulnar joint dislocations in any of the patients.

Exclusion criteria were multiple fractures, less than 12 months of follow-up, bilateral distal radius fractures, intra-articular fractures, current use of anticoagulant medications or non-steroidal anti-inflammatory drugs (NSAIDs), presence of existing osteoarthritis or sequelae from previous trauma to the upper extremity that may limit the patient's range of motion and function prior to injury, infection, tumor, crystal arthropathies, anemia, intense joint effusion. Inclusion and exclusion criteria were summarized in **Table 1**.

The power analysis of this study was calculated based on the sample size studies of previous studies. A sample size of 90 was required for 95% power in a 95% confidence interval. All patients were selected according to pre-defined and established inclusion and exclusion criteria.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age > 60 years	Intra-articular fractures (AO/OTA classification type C),
Dorsally displaced, extra-articular fracture (AO/OTA classification type A3)	Volarly displaced fractures (Smith and AO type-B fractures)
Unstable fractures >20 of dorsal angulation of the articular surface on the lateral radiographic view	Open, bilateral and pathological fractures
Isolated injury	Fractures associated with neurovascular injury
	Bone and joint diseases that could interfere with rehabilitation
	Patients presenting more than a week after injury
	Follow-up shorter than 12 months

Clinical Evaluation

The patients were evaluated in terms of injury mechanism, loss of function, pain and wrist deformity. It is noted which hand is dominantly used. In order to better understand the demands on the upper extremities of the elderly patient, independence in performing activities of daily living was investigated. This is very important and can influence treatment decisions. Systematic examination of the hand and wrist was evaluated from distal to proximal. The vascular status of the hand, capillary filling, radial and ulnar pulses were carefully noted. In the sensory examination, two-point discrimination values, the ability to perceive light touch in the median, ulnar and radial nerve regions were noted. Since acute carpal tunnel syndrome is reported in 5.4% to 8.6% of all distal radius fractures, any presence of paresthesia or numbness in the median distribution was carefully evaluated (14). The presence of open fracture, ecchymosis, edema or angular deformities, laceration or skin tears were also carefully noted. Since the skin and subcutaneous soft tissue are thin in the elderly patient group, skin rupture can be seen very commonly. Particular care was taken not to damage these tissues during closed reduction.

Radiographic Evaluation

Anteroposterior, lateral and oblique radiographs of the hand and wrist were taken before and after the procedure in all cases. Radial inclination, radial height and volar tilt radiological parameters were evaluated. Radiographs of the forearm and elbow were also seen to detect more proximal injuries or elbow instability. After CRPC and CRPP, radiographs were taken documenting the appropriate restoration of radiological parameters. Computed tomography (CT) has been used as a diagnostic aid or to better understand fracture patterns and aid in surgical planning.

Treatment Methods and Follow-up

The latest clinical practice guideline for distal radius fractures of the American Academy of Orthopedic Surgeons (AAOS) states that operative treatment in patients over 65 years of age does not differ significantly in long-term outcomes compared to non-operative treatment (15). The important factors that we paid attention to when planning treatment for patients were fracture pattern, radiographic parameters, age, hand control, and occupation. We primarily applied closed reduction and long arm splinting to extra-articular distal radius fractures over 65 years of age who applied to our institutions. If there is no displacement in the fracture line after one week in the patients we follow up with one-week intervals, we switch to short arm cast (**Figure 1A**). We applied the CRPP procedure to patients who were not reduced or had loss of reduction in the follow-ups (**Figure 1B**).

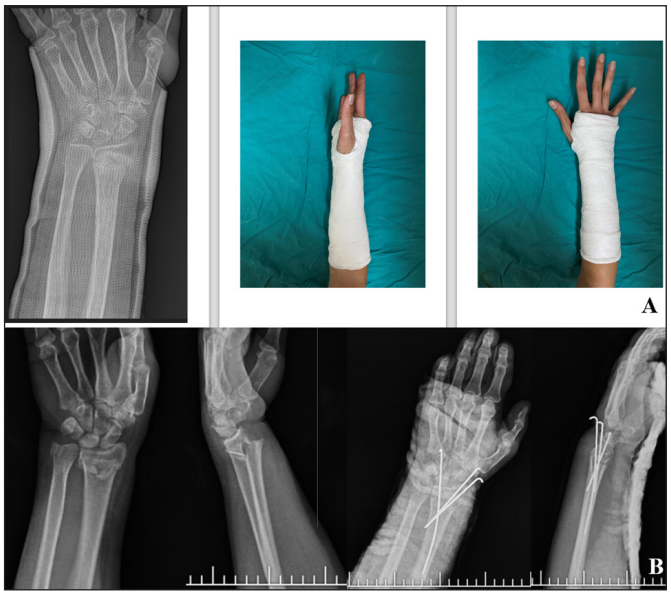

Figure 1. A) Clinical and radiological images of the patient treated with closed reduction plaster casting. **B)** Pre- and post-treatment radiological images of the patient treated with closed reduction percutaneous pinning.

The splint and plaster cast end on the palmar side of the hand, just proximal to the metacarpal heads, and we allowed early finger range of motion to prevent stiffness and preserve mobility. Conversion of a long arm splint to a short arm cast reduces the overall volume of the splint and allows for increased range of motion and therefore less stiffness. However, it is necessary to be very careful during the transition to the short arm cast. During this procedure, the fracture line may be displaced. This risk is higher in elderly patients (16).

Closed reduction of the fracture was achieved under control radiographies. In the closed reduction group, three-point fixation was obtained in a well-molded, long-arm cast. A long arm cast with the wrist in neutral

flexion/extension and the elbow flexed to 90° in the neutral rotation was carried out initially, converted to a short arm cast in the third week, and then removed in the fifth week.

We applied the CRPP procedure to patients who were not reduced or had loss of reduction in the follow-ups. Under general anesthesia, the fracture was reduced with traction and volar angulation under fluoroscopic control. One pin was implanted from the radial styloid and the other from the tubercle of Lister in a crossing the fracture manner under fluoroscopic guidance. The pins were left protruding percutaneously and the wrist was then immobilized in a well-molded short-arm cast.

All patients had similar follow-up protocols. In the CRPC group, elbow and shoulder exercises were started with the conversion to a short arm cast in the third week. The plasters were removed after five weeks. In the CRPP group, elbow and shoulder exercises were started immediately. The wires were removed after six weeks. Clinical and radiological reviews were performed every week until the plaster was removed.

During this period, the patients were followed up on a weekly basis. Optimal rehabilitation options after treatment of distal radius fractures are controversial. It is stated that there is no difference in the results between the home exercise program and the supervised treatment after the treatment of distal radius fractures, and the preference and compliance of the patient is important (15). A standard exercise program was applied to our patients after plaster follow-up by a certified hand therapist in our clinics. Early finger range of motion has been applied in all patients as it will help prevent stiffness, which is an important complication of immobilization following distal radius fractures.

The intensity of pain was recorded on a visual analog scale from 0 to 10. The range of movement of the wrist was measured using a goniometer and expressed as a percentage of the normal contralateral side (17). Grip strength was assessed by a Jamar dynamometer (Therapeutic Equipment Corporation, Clinton, New Jersey), and the mean of three readings was expressed as a percentage of the normal contralateral side, allowing 10% less for the non-dominant side (18, 19). The ability to perform unilateral and bilateral activities of daily living (ADL) was also scored (17-20).

Standardized anteroposterior and lateral radiographs of the wrist were taken with the forearm in neutral rotation (21). The radiographic results were evaluated in terms of radial inclination, palmar tilt, radial height, and ulnar variance in the last follow-up radiograms. To minimize interobserver error, all results were assessed by one surgeon. Posttraumatic arthritis was evaluated at radiological follow-up with narrowing of the radioscapholunate joints. The dorsal angulation of the distal radius expressed as the number of degrees from the neutral position, the radial inclination and length, and ulnar variance were then measured (22-25).

Statistical Analysis

The data obtained were evaluated using SPSS v.20 software (Statistical Package for Social Sciences). A value of $p<0.05$ was considered statistically significant. In the comparison of two independent groups showing normal distribution, two Independent t-tests were performed, and One-way Analysis of Variance (One Way Anova) was used to compare more than two groups. The Kruskal Wallis H test was performed to investigate differences between more than two independent groups that did not conform to normal distribution. When there was a difference between the groups, to determine from which group or groups this difference originated, the Mann Whitney U test was used to compare the two groups. A new limit level was calculated by dividing the 0.05 value of Type-1 error limit level to the number of comparisons. A new p value was obtained using post-hoc Bonferroni correction.

RESULTS

Age, gender, the AO classification, dominant hand involvement, soft tissue swelling, and smoking habits were noted. Basic characteristics of patients with distal radius fractures are presented in **Table 2**. There was no significant difference between the treatment groups in terms of these variables. The mean follow-up period was 19.8 months (range, 12-29 months; SD=11.0) in the CRPC group and 18.6 months (range, 12-26 months; SD=10.9) in the CRPP group.

Table 2: Baseline characteristics of patients with distal radius fractures

Characteristics	CRPCF(n:51)	CRPPF(n:44)	P value
Mean age	72.98± 4.36	71.36± 4.29	.061
AO/OTA Classification type, A2 vs A3	20/31	18/26	.866
Gender, F/M	30/21	25/19	.843
Dominant hand Involvement (yes/no)	27/23	29/15	.240
Smoker (yes/no)	19/32	18/26	.715

The mean range of motions and grip strength were protected in the first-year follow-up. The results are summarized in **Table 4**. There was no statistically significant difference among the groups.

Table 3: Mean range of movement and grip strength (SD) for both groups at the final follow-up expressed as a percentage of the normal side

	CRPCF	CRPPF	P value
Flexion	82.58±30.50	81.05±26.42	.483
Extension	95.27±17.04	93.43±15.02	.912
Pronation	94.08±23.67	93.6±29.75	.498
Supination	86.95±23.36	87.06±27.61	.849
Radial deviation	87.77±27.10	89.66±26.77	.528
Ulnar deviation	83.89±24.09	88.38±21.13	.896
Grip strength	94.06±26.17	95.49±31.41	.681

Table 4: Mean (SD) scores for functional assessment for both groups at the final follow-up

	CRPCF	CRPPF	P Value
Activities of daily living			
Unilateral	6.12±1.07	6.43±1.02	.144
Bilateral	17.14±1.96	17.43±1.78	.357
Pain score	1.49±1.12	1.34±1.07	.548
SF-36			
Physical score	83.16±8.10	83.30±8.82	.857
Mental score	87.15±9.6	89.17±8.5	.876

The patients performed well in terms of daily activities, pain, and mental status after treatment (**Table 5**). There was no statistically significant difference between the groups.

There was no statistically significant difference among the groups in terms of radiological parameters. Results are summarized in **Table 5**.

Table 5: Mean radiological measurements (SD) for the two treatment groups

Measurement	CRPCF	CRPPF	P value
Palmar angulation			
Normal contralateral wrist	12.29±3.95	12.48±3.96	.860
Preoperative	-1.49±14.20	-2.1±12.33	.725
Postoperative	15.67±2.48	16.65±3.61	.832
1-Year	12.88±4.81	14.70±3.72	.091
Radial length (mm)			
Normal contralateral wrist	11.33±1.99	10.95±2.05	.369
Preoperative	2.45±3.72	3.73±3.05	.941
Postoperative	10.45±1.69	11.17±1.54	.461
1-Year	10.25±1.74	10.54±1.59	.383
Radial inclination			
Normal contralateral wrist	20.66±1.54	21.13±1.44	.141
Preoperative	3.23±3.05	2.45±3.71	.346
Postoperative	20.38±2.01	21.63±1.86	.964
1-Year	18.25±1.74	19.54±1.59	.883
Ulnar variance (mm)			
Normal contralateral wrist	2.09±1.17	2.14±1.19	.441
Preoperative	1.3±1.62	1.22±1.93	.096
Postoperative	1.96±0.87	2.09±1.04	.546
1-Year	1.85±0.95	2.01±0.54	.354

Five patients had pin-tract infections in the CRPP group and all of them were treated with oral antibiotics. Eight patients in the CRPC group had reduction loss in the first week and they were treated with CRPPF. Although these patients were successfully treated, since they did not fit any of the groups, they were excluded from the study. No nonunion or other significant complication was observed among the patients in this study.

DISCUSSION

The ideal treatment of extra-articular distal radius fractures is still debatable. CRPC and CRPP continue to be very important treatment modalities for distal extra-articular radius fractures especially in elderly patients. Both of these therapeutic modalities have benefits and drawbacks in comparison. Most studies define the elderly as patients between the ages of 50 and 75 (7, 10, 11). In this study, patients aged 65 and over were defined as elderly. There is no high-quality scientific data is available about the appropriate treatment technique for elderly patient population, despite the high occurrence of displaced distal radius fractures and the significant potential consequences of inadequate therapy (26). Our goal was to examine the clinical and radiological outcomes of CRPC and CRPP for the treatment of distal radius fractures in patients over 65. Our study showed that in the patient population aged 65 and over, percutaneous pinnig after closed reduction was not superior to plaster casting in the treatment of extra-articular distal radius fractures. Both treatment modalities are characterized by low complication rates and reasonable clinical outcomes.

Treatment often depends on the nature and severity of the fracture, the patient's age and general condition, the surgical indication, and also on the surgeon's technical skill (27). According to the distal radius fracture guidelines supported by the AAOS, fractures based on instability criteria, such as post-reduction radial shortening of> 3 mm, dorsal tilt of> 10 degrees, or intra-articular displacement or step-off of> 2 mm, should be treated surgically (28). Regrettably, these guidelines don't offer precise indications or/and suggestions for the management of elderly patients.

Anatomical reduction with closed manipulation is achieved, but there is no agreement on the most appropriate method to ensure the continuity of reduction in unstable fractures. A meta-analysis reports that conservative treatment with cast-immobilization is adequate in elderly patients (29), but another study concluded that anatomical reduction and fixation with a volar plate is the best option (30). On the other hand, crossfire study found no difference between conservative treatment and cast immobilization in the elderly (31). A recent meta-analysis found no difference between cast

immobilization and several surgical techniques (32). While volar locking plates were found to be superior in terms of DASH scores, this superiority is minimal and does not have clinical importance (33). In summary, the literature is full of conflicts on the ideal treatment of distal radius fractures.

Perfect anatomical reduction of distal radius fractures is thought to be strongly associated with perfect clinical outcomes. Loss of volar tilt is found to be associated with midcarpal instability (34). A 2.5 mm increase in ulnar variance will increase the load on the ulnocarpal joint by 18 to 42% (35). On the other hand, negative ulnar variance is associated with avascular necrosis of the lunate (36). As a result, it is useful to pay attention to anatomical reduction during the treatment process.

Despite the worse radiographic outcomes associated with CRPC, many studies have shown that differences in functional outcomes compared with those treated surgically are not clinically significant (37). Evidence of a relationship between radiological reduction criteria and functional outcomes in elderly people is still equivocal (38). According to a recent study, the most important risk factor for radial collapse following open reduction and internal fixation with a volar plate is post-operative ulnar positive deformity. However, there were no statistically significant differences in range of motion, grip strength, or pain in elderly patients (39). The reduced functional demand in the upper limbs assumed to be connected to aging may be the cause of the lack of correlation between radiographic and functional results. Certain patient-related factors have been demonstrated to be significantly associated with functional results, in contrast to anatomical or radiological data. These variables include the amount of physical activity, anxiety brought on by pain, pain catastrophizing, and the intensity of acute pain (40). Considering these criteria in this study constitutes one of the strengths of the study.

Although several studies on the use of percutaneous K-wires for the stabilization of distal radial fractures have been published (41-44), their use in an elderly population remains uncertain. These studies include different fracture patterns and various treatment modalities, and controlled trials are lacking. Stoffelen and Broos (45) conducted a prospective, randomized trial comparing closed reduction with intrafocal pinning for extra-articular fractures. They found no significant difference in the outcome between the two groups. However, their series included young patients with both stable and unstable fractures and excluded those older than 80 years of age. In a recent meta-analysis, the patient population aged 60 and over showed no clinical or statistical difference between plaster immobilization and K-wire immobilization at 1-year follow-up (37). This conclusion is in line with our research.

In our study, we found that both plaster casting and percutaneous pinning are suitable options for the treatment of distal radius in the elderly with relatively low complication rates. There is no significant difference between CRPC and CRPP in terms of clinical and radiological results. Given the increased life expectancy and low functional demands in the elderly population, maintaining a good quality of life with CRPC and CRPP treatments may be as important as achieving optimal recovery of hand function with other surgical treatments. In addition, the decision to expose patients to even a single surgery in this age group must be made carefully. In this study, it was concluded that CRPC and CRPP treatments may still be a good option for patients older than 65 years of age.

This study has its own limitations. First of all, the retrospective nature of this study may lead to selection bias. It also made randomization impossible, but there were no significant differences between our groups in terms of age, gender, type of fracture, smoking habit, and dominant hand involvement. Our second limitation was the limited population size. A prospective randomized study performed on a wider group may result in a more accurate and valuable conclusion.

CONCLUSION

Percutaneous pinning after closed reduction was not found to be superior to plaster casting in the treatment of extra-articular distal radius fractures in the aged 65 and older patient population. Both treatment modalities are characterized by low complication rates and reasonable clinical results. Further prospective randomized studies will enhance our knowledge of distal radius fractures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Research Ethics Committee (Date: 07.02.2019, Decision No: 2019/114).

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. Jupiter JB. Fractures of the distal end of the radius. J Bone Joint Surg Am 1991; 73: 461-9.
2. Nellans KW, Kowalski E, Chung KC. The epidemiology of distal radius fractures. Hand Clin 2012; 28: 113-25.
3. Mensforth RP, Latimer BM. Hamann-Todd Collection aging studies: osteoporosis fracture syndrome. Am J Phys Anthropol 1989; 80: 461-79.
4. Randomised TC, Group OSoSfFitDRitES. Surgical Plating vs Closed Reduction for Fractures in the Distal Radius in Older Patients: A Randomized Clinical Trial. JAMA Surgery 2021; 156: 229-37.
5. Chhabra AB, Yildirim B. Adult Distal Radius Fracture Management. JAAOS - Journal of the American Academy of Orthopaedic Surgeons 2021; 29: e1105-e16.
6. Colles A. On the fracture of the carpal extremity of the radius. Edinb Med Surg J. 1814;10:181. Clin Orthop Relat Res 2006; 445: 5-7.
7. Arora R, Lutz M, Deml C, Krappinger D, Haug L, Gabl M. A prospective randomized trial comparing nonoperative treatment with volar locking plate fixation for displaced and unstable distal radial fractures in patients sixty-five years of age and older. J Bone Joint Surg Am 2011; 93: 2146-53.
8. Horne JG, Devane P, Purdie G. A prospective randomized trial of external fixation and plaster cast immobilization in the treatment of distal radial fractures. J Orthop Trauma 1990; 4: 30-4.
9. Handoll HH, Madhok R. Surgical interventions for treating distal radial fractures in adults. Cochrane Database Syst Rev 2003; 3: Cd003209.
10. Marcheix P-S, Dotzis A, Benkö P-E, Siegler J, Arnaud J-P, Charissoux J-L. Extension fractures of the distal radius in patients older than 50: a prospective randomized study comparing fixation using mixed pins or a palmar fixed-angle plate. Journal of Hand Surgery (European Volume) 2010; 35: 646-51.
11. Brogren E, Hofer M, Petranek M, Dahlin L, Atroshi I. Fractures of the distal radius in women aged 50 to 75 years: natural course of patient-reported outcome, wrist motion and grip strength between 1 year and 2–4 years after fracture. Journal of Hand Surgery (European Volume) 2011; 36: 568-76.
12. Müller ME, Nazarian S, Koch P, Schatzker J. The comprehensive classification of fractures of long bones: Springer Science & Business Media; 2012.
13. Frykman G. Fracture of the distal radius including sequelae, shoulder-hand syndrome, disturbance in the distal radio-ulnar joint and impairment of nerve function; A clinical and experimental study. Acta Orthop Scand 1967; 18: 108.
14. Niver GE, Ilyas AM. Carpal tunnel syndrome after distal radius fracture. Orthopedic Clinics 2012; 43: 521-7.
15. Kamal RN, Shapiro LM. American Academy of Orthopaedic Surgeons/American Society for Surgery of the Hand Clinical Practice Guideline Summary Management of Distal Radius Fractures. JAAOS - Journal of the American Academy of Orthopaedic Surgeons 2022; 30: e480-e6.
16. Makhni EC, Ewald TJ, Kelly S, Day CS. Effect of patient age on the radiographic outcomes of distal radius fractures subject to nonoperative treatment. J Hand Surg Am 2008; 33: 1301-8.
17. McQueen M, Hajducka C, Court-Brown C. Redisplaced unstable fractures of the distal radius: a prospective randomised comparison of four methods of treatment. The Journal of Bone and Joint Surgery British volume 1996; 78: 404-9.
18. Bechtol CO. Grip test: the use of a dynamometer with adjustable handle spacings. JBJS 1954; 36: 820-32.
19. Crosby CA, Wehbé MA. Hand strength: normative values. The Journal of hand surgery 1994; 19: 665-70.
20. Sheehan N, Sheldon F, Marks D. Grip strength and torquometry in the assessment of hand function in patients with rheumatoid arthritis. Rheumatology 1983; 22: 158-64.
21. Jung J, Baek G, Kim J, Lee Y, Chung M. Changes in ulnar variance in relation to forearm rotation and grip. The Journal of Bone and Joint Surgery British volume 2001; 83: 1029-33.
22. Young BT, Rayan GM. Outcome following nonoperative treatment of displaced distal radius fractures in low-demand patients older than 60 years. The Journal of hand surgery 2000; 25: 19-28.
23. McQueen M. Redisplaced unstable fractures of the distal radius: a randomised, prospective study of bridging versus non-bridging external fixation. The Journal of Bone and Joint Surgery British Volume 1998; 80: 665-9.
24. Van der Linden W, Ericson R. Colles' fracture. How should its displacement be measured and how should it be immobilized? The Journal of Bone and Joint surgery American Volume 1981; 63: 1285-8.
25. Palmer AK, Glisson RR, Werner FW. Ulnar variance determination. The Journal of hand surgery 1982; 7: 376-9.
26. Walenkamp MM, Goslings JC, Beumer A, et al. Surgery versus conservative treatment in patients with type A distal radius fractures, a randomized controlled trial. BMC Musculoskelet Disord 2014; 15: 90.
27. Ducournau F, Meyer N, Xavier F, Facca S, Liverneaux P. Learning a MIPO technique for distal radius fractures: Mentoring versus simple experience versus deliberate practice. Orthop Traumatol Surg Res 2021; 107: 102939.
28. Young BT, Rayan GM. Outcome following nonoperative treatment of displaced distal radius fractures in low-demand patients older than 60 years. J Hand Surg Am 2000; 25: 19-28.
29. Haane C, Mardin WA, Schmitz B, et al. Pancreatoduodenectomy—current status of surgical and perioperative techniques in Germany. Langenbeck's archives of surgery 2013; 398: 1097-105.
30. Bruyere A, Vernet P, Botero SS, Igeta Y, Hidalgo Diaz JJ, Liverneaux P. Conservative treatment of distal fractures after the age of 65: a review of literature. Eur J Orthop Surg Traumatol 2018; 28: 1469-75.
31. Ian AH, Justine MN, Lawson A, et al. A combined randomised and observational study of surgery for fractures in the distal radius in the elderly (CROSSFIRE)—a study protocol. BMJ open 2017; 7: e016100.
32. Van Oijen GW, Van Lieshout EM, Reijnders MR, Appalsamy A, Hagenaars T, Verhofstad MH. Treatment options in extra-articular distal radius fractures: a systematic review and meta-analysis. Eur J Trauma Emerg Surg 2021: 1-16.
33. Chaudhry H, Kleinlugtenbelt YV, Mundi R, Ristevski B, Goslings J, Bhandari M. Are volar locking plates superior to percutaneous K-wires for distal radius fractures? A meta-analysis. Clinical Orthopaedics and Related Research® 2015; 473: 3017-27.
34. Taleisnik J, Watson HK. Midcarpal instability caused by malunited fractures of the distal radius. The Journal of hand surgery 1984; 9: 350-7.
35. Palmer AK. The distal radioulnar joint: anatomy, biomechanics, and triangular fibrocartilage complex abnormalities. Hand Clin 1987; 3: 31-40.
36. Bonzar M, Firrell JC, Hainer M, Mah ET, MCCABE SJ. Kienböck disease and negative ulnar variance. JBJS 1998; 80: 1154-57.
37. Gutiérrez-Espinoza H, Araya-Quintanilla F, Olguín-Huerta C, et al. Effectiveness of surgical versus conservative treatment of distal radius fractures in elderly patients: A systematic review and meta-analysis. Orthop Traumatol Surg Res 2022; 108: 103323.
38. Mulders MAM, Detering R, Rikli DA, Rosenwasser MP, Goslings JC, Schep NWL. Association Between Radiological and Patient-Reported Outcome in Adults With a Displaced Distal Radius Fracture: A Systematic Review and Meta-Analysis. J Hand Surg Am 2018; 43: 710-9.e5.

39. Cheng MF, Chiang CC, Lin CC, Chang MC, Wang CS. Loss of radial height in extra-articular distal radial fracture following volar locking plate fixation. Orthop Traumatol Surg Res 2021; 107: 102842.
40. Hevonkorpi TP, Launonen AP, Raittio L, et al. Nordic Innovative Trial to Evaluate OsteoPorotic Fractures (NITEP-group): non-operative treatment versus surgery with volar locking plate in the treatment of distal radius fracture in patients aged 65 and over - a study protocol for a prospective, randomized controlled trial. BMC Musculoskelet Disord 2018; 19: 106.
41. Ring D, Jupiter JB. Percutaneous and limited open fixation of fractures of the distal radius. Clinical Orthopaedics and Related Research (1976-2007) 2000; 375: 105-15.
42. Clancey GJ. Percutaneous Kirschner-wire fixation of Colles fractures. A prospective study of thirty cases. The Journal of Bone and Joint surgery American Volume 1984; 66: 1008-14.
43. Rayhack JM. The history and evolution of percutaneous pinning of displaced distal radius fractures. The Orthopedic clinics of North America 1993; 24: 287-300.
44. Rodríguez-Merchán EC. Plaster cast versus percutaneous pin fixation for comminuted fractures of the distal radius in patients between 46 and 65 years of age. J Orthop Trauma 1997; 11: 212-7.
45. Stoffelen D, Broos P. Closed reduction versus Kapandji-pinning for extra-articular distal radial fractures. J Hand Surg Am 1999; 24: 89-91.

Original Article

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Comparison of predictive scoring systems in patients hospitalized in the internal medicine intensive care unit

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ABSTRACT

Aim: Various scoring systems have been developed to predict mortality, disease severity, and length of stay of patients in intensive care units. It is important to demonstrate the validity of these scores in the society in which they are used. This study aims to evaluate the effects of The Acute Physiologic and Chronic Evaluation (APACHE)-II, APACHE-IV, The Simplified Acute Physiologic Score (SAPS), and Mortality Prediction Model (MPM0) scores on mortality in the internal medicine intensive care unit.

Material and Method: The patients who were followed up in an internal medicine intensive care unit between June 2021 and December 2021 in a tertiary hospital in Turkey were included in this study. The scores were calculated at the time they were admitted to the intensive care unit. 115 patients who were followed up in the internal medicine intensive care unit for 6 months were included. The patients were divided into two groups alive or deceased. 52 (45.2%) patients in the survivor group and 63 (54.8%) patients in the deceased group were included. Patients received no study-related medical intervention.

Results: When all four prognostic scoring systems were analyzed according to the median cut-off values, rising values were related to mortality with statistical significance ($p<0.001$). Hosmer-Lemeshow (HL) test p values in the univariate logistic regression model (higher than the others) showed that the APACHE IV had a better calibration than the other scores. However, the H-L p values of all scores were above 0.05.

Conclusion: Although all scoring systems are good predictors of mortality in patients in internal medicine intensive care units, none of them is superior to the other for mortality prediction.

Keywords: APACHE, SAPS, MPMO

INTRODUCTION

Various scoring systems have been developed to predict mortality, disease severity, and length of stay of patients in intensive care units. The purpose of using these scoring systems is to estimate mortality when patients are admitted to the intensive care unit and to consider this during the follow-up period.

These scoring systems were developed by using data obtained from large cohorts who were followed in intensive care units. Automatic calculators are available for each system that come into use after the validation. The three most frequently used scoring systems in general intensive care units are The Acute Physiologic and Chronic Evaluation (APACHE), The Simplified Acute Physiologic Score (SAPS), and Mortality Prediction Model (MPM0) (1-5). The new versions of them are being developed as a result of the updates (6).

The APACHE scoring system includes 129 physiological and laboratory variables of the patients. The worst values of the patient during the first 24 hours of intensive care unit admission are used to calculate the APACHE score (1). The latest version currently used is APACHE-IV, which has been shown to predict mortality better than the previous version (1).

The SAPS is measured by evaluating approximately 20 parameters considering the worst values in the first 24 hours of the patient's admission to the intensive care unit. Although the latest version is SAPS-3, there are also studies suggesting that it overestimates mortality (3,4,7). Therefore, SAPS-2 is still being used in our center.

The MPM0 scoring system evaluates the clinical and physiological data at the time of admission to the intensive care unit. The current version of this system is MPM0-III, and its effectiveness has been demonstrated by calibration and external validation (5).

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Scoring systems best represent the society in which they were developed. For this reason, it is important to perform external validation according to both the center and the region and to demonstrate its reliability in the society in which it is used (3,4). General intensive care units admit patients with diverse diagnoses. Post-operative patients, trauma patients, patients with a diagnosis of acute coronary syndrome and revascularization therapy, patients with acute neurological problems, and general internal medicine diseases may all be followed in general intensive care units. But usually intensive care units are classified according to the patient's diagnoses. This fact may differ from region to region.

This study aims to evaluate the effects of APACHE-II, APACHE-IV, SAPS-2, and MPM0 -III scores on mortality in patients followed by an internal medicine specialist, in a tertiary general intensive care unit in Turkey and to determine which scoring system is better and more reliable for this patient group.

MATERIAL AND METHOD

The study was carried out with the permission of Samsun Research and Training Hospital Non-interventional Clinical Researches Ethics Committee (Date: 25.08.2021, Decision No: GOKA/2021/15/3). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

115 patients who were followed up in an internal medicine intensive care unit between June 2021 and December 2021 in a tertiary hospital in Turkey were included in this study. All patients over the age of 18 who were hospitalized and followed up in the general intensive care unit by an internal medicine specialist were included.

Trauma patients, post-operative patients, hospitalized patients with a neurological diagnosis, and patients who were hospitalized but admitted to the 1st level intensive care unit were excluded from the study. A total of 115 patients who met these criteria during the 6-month follow-up period were included in the study.

The patient's age, gender, comorbidities, medications, and diagnosis of admission to the intensive care unit were reviewed retrospectively from the patient files. The physical examination findings of the patients, arterial blood pressure, heart rate, and laboratory values at the time of admission to the intensive care unit were recorded. The length of stay and whether there was any blood culture positivity during the hospitalization were recorded.

APACHE-II, APACHE-IV, SAPS-2, and MPM0 -III scores were calculated at the time they were admitted to the intensive care unit (8-11). The patients were divided into two groups according to the way they were discharged from the intensive care unit, those who were transferred to the service as alive and those who died. 52 (45.2%) patients in the survivor group and 63 (54.8%) patients in the nonsurvivor group were included.

Hospitalization diagnoses and comorbidities, which caused a significant difference between the two groups, were analyzed.

Statistical Analysis

SPSS program (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Normally distributed continuous variables were expressed as mean ± standard deviation, while non-normally distributed continuous variables were expressed as median (lowest-highest). Categorical variables were expressed as n (%). The Chi-square test and Fischer's exact test were used to compare the categorical variables between groups. Kaplan-Meier survival analysis was done to investigate the effect of scoring systems on survival. Logistic regression analysis and Hosmer-Lemeshow (HL) test were done to investigate the effect of scoring systems on mortality.

RESULTS

A total of 115, 57 women and 58 men were included in the study. The mean age of the patients was 70 ± 15 years. The median length of stay in the intensive care unit was 4 (1-71) days. The admission diagnoses of the patients hospitalized in the intensive care unit were as follows: 21 (18.3%) acute renal failure, 22 (19.1%) gastrointestinal bleeding, 15 (13%) pneumonia, 5 (4.3) electrolyte imbalance, 2 (1.7 %) malnutrition, 13 (11.3%) sepsis, 11 (9.6%) respiratory failure, 26 (22.6) other diagnoses.

All-cause intensive care mortality rate was found to be 54.8%. Mortality rates according to the admission diagnosis were as follows: acute renal failure 23.8%, sepsis 20.6%, pneumonia 20.6%, gastrointestinal bleeding 11.1%, respiratory failure 6.3%, electrolyte imbalance 3.2%, malnutrition 3.2%, and other diagnoses 11.1%.

Demographic and clinical characteristics of the study population are given in **Table 1**. There was no statistically significant difference between the survivor and the nonsurvivor group in terms of gender. The mean age of the nonsurvivors was statistically greater than that of the survivors. It was determined that all 4 mortality scores were statistically higher in the nonsurvivors. In terms of hospitalization diagnoses, gastrointestinal bleeding and other diagnoses were statistically more frequent in survivors while pneumonia and sepsis were more common in nonsurvivors. The frequencies of acute renal failure, electrolyte imbalance, malnutrition, and respiratory failure were statistically similar between

the two groups. When evaluated in terms of comorbid conditions, the frequency of malignancy was statistically higher in nonsurvivors. There was no statistically significant difference between the two groups in terms of other comorbidities.

Table 1. Demographic and clinical characteristics of the study

	Survivors (n: 52)	Nonsurvivors (n: 63)	p
Male sex, n (%)	30 (58)	28 (44)	0.157
Age (years)	64 ± 17	74 ± 11	0.001
Length of ICU stay (days)	3.5 (1-71)	6 (1-66)	0.275
APACHE II score	35.6 (6.6-95.4)	78.6 (14.6-98)	< 0.001
APACHE IV score	17.7 (1.1-77.5)	57.3 (10-95.9)	< 0.001
SAPS II score	10.6 (1.3-83.8)	59.8 (4.7-99.1)	< 0.001
MPM0 III score	19.6 (1.58-88.5)	49 (6-95.7)	< 0.001
Admission Diagnosis			
Acute renal failure, n (%)	6 (11.5)	15 (23.8)	0.090
Gastrointestinal bleeding, n (%)	15 (28.8)	7 (11.1)	0.016
Pneumonia, n (%)	2 (3.8)	13 (20.6)	0.008
Electrolyte imbalance, n (%)	3 (5.8)	2 (3.2)	0.657
Malnutrition, n (%)	0 (0)	2 (3.2)	0.500
Sepsis, n (%)	0 (0)	13 (20.6)	0.001
Respiratory Failure, n (%)	7 (13.5)	4 (6.3)	0.197
Others, n (%)	19 (36.5)	7 (11.1)	0.001
Comorbidities			
Diabetes mellitus, n (%)	21 (40.4)	25 (39.7)	0.939
Chronic renal failure, n (%)	9 (17.3)	16 (25.4)	0.295
COPD, n (%)	6 (11.5)	8 (12.7)	0.850
Congestive heart failure, n (%)	12 (23.1)	21 (33.3)	0.226
Dementia, n (%)	8 (15.4)	16 (25.4)	0.189
Hypertension, n (%)	28 (53.8)	35 (55.6)	0.855
Malignancy, n (%)	3 (5.8)	24 (38.1)	< 0.001

Multiple Logistic Regression

When the effects of APACHE II, APACHE IV, SAPS 2, and MPM0-III scores on mortality were analyzed by multiple logistic regression analysis independent of clinical parameters not used in their score-based algorithms, the OR and 95% CI values were determined as follows. APACHE II: 1.053 and 1.030-1.077 (independent variables: acute renal failure, gender, diabetes mellitus, admission diagnoses excluding dementia), APACHE IV: 1.085 and 1.051-1.114 (independent variables: gender, diabetes mellitus, congestive heart failure, hypertension, dementia, chronic obstructive pulmonary disease), SAPS 2: 1.071 and 1.039-1.104 (independent variables: gender, admission diagnoses excluding acute renal failure and gastrointestinal bleeding, diabetes Mellitus, hypertension, dementia, chronic obstructive pulmonary disease) and MPM0-III: 1.071 and 1.041-1.101 (independent variables: Gender, admission diagnoses excluding acute renal failure and gastrointestinal bleeding, diabetes mellitus, hypertension, dementia, and chronic obstructive pulmonary disease).

Univariate logistic regression analysis, Hosmer-Lemeshow (HL) score results are given in **Table 2**. HL test p values in the univariate logistic regression model (higher than the others) showed that the APACHE IV had a better calibration than the other scores. However, the H-L p values of all scores were above 0.05.

Table 2. Univariate logistic regression analysis, Hosmer-Lemeshow (HL) score results

n: 115	APACHE II	APACHE IV	SAPS II	MPM0-III
Logistic regression				
OR (95% CI)	1.049 (1.031-1.067)	1.071 (1.046-1.097)	1.056	1.057
H-L test				
x^2	12.8	6.6	6.4	10.2
Df	7	8	7	8
P	0.076	0.583	0.495	0.252

DISCUSSION

It has been shown that APACHE-IV, SAPS-3, and MPM0 -III are reliable predictive models to predict mortality, length of stay, and prognosis of patients who were followed in the intensive care unit (12).

Although APACHE-IV is the last version of the APACHE scoring system, APACHE-II is still used in some centers as well as our center (13,14).

However, these scoring systems do not have the same accuracy in every disease group. For this reason, studies are carried out about which scoring system is more reliable in intensive care for special patient groups. For example, in a study on patients hospitalized in the gastroenterology intensive care unit, APACHE-II, SAPS-II, and Sequential Organ Failure Assessment (SOFA) scores were compared, and all three were found to be associated with mortality in this patient group. The system with the most perfect prognostic predictive feature is stated as the SOFA score in this patient group (13). In our study, the frequency of gastrointestinal bleeding as admission diagnosis was 19.1% and the mortality rate of this patient group was 11.1%. This result is greater than the overall mortality score (5.3%) of the previously mentioned study (13). In another study conducted among patients in the neurosurgical intensive care unit APACHE II score had a poor performance to predict hospital mortality (14).

In our study, the cut-off values of SAPS-II and APACHE-II score to predict mortality were 23.0 and 73.0 respectively. In a recent study including 174 patients in the medical

intensive care unit, SAPS II >50.5 and APACHE II >27.5 can predict the risk of mortality in these patients. Patients with an admission diagnosis of sepsis had the highest hospital mortality (15). In our study, the all-cause intensive care mortality rate was 54.8% and higher than the mentioned study. The mortality rate of patients with sepsis was 20.6%. According to the diagnosis of hospitalization, the highest mortality was found in sepsis patients, which was consistent with the results of the related study (15).

In another recent study that includes traumatic brain injury patients, the APACHE II had poor power than the INCNS scoring system to predict mortality in this patient group. The researchers thought that INCNS could be considered a usable prognostic model for Turkish people (16).

Sepsis is a common diagnosis among patients hospitalized in the internal medicine intensive care unit, and in our study, 11.1% of the patients were found to be admitted to the intensive care unit with the diagnosis of sepsis. In a study investigating mortality predictive systems in patients hospitalized in the intensive care unit with the diagnosis of sepsis, it was shown that a high SOFA score and APACHE-II were associated with mortality (17). In another study, in which sepsis patients were included and 140 patients were admitted, high SOFA and quick SOFA scores were found to be risk factors for the severity of the patients and worsening of the prognosis (18).

In a prospective study of 300 patients hospitalized in the cardiac intensive care unit, APACHE-II and SOFA scores were compared and both of those scoring systems were found to be good predictors for mortality. In that study, the APACHE-II score was also related to 6 months mortality (19). There was not any patient with a cardiac admission diagnosis in our study group.

These studies show that the same scoring system may not be valuable for determining intensive care mortality rates in every patient group and community. For this reason, we think that it is important to conduct separate analyzes for intensive care units where certain diagnoses are clustered and followed. In our study, the data of 115 patients, who were hospitalized in the intensive care unit followed only by internal medicine specialists and included the common disease groups followed in the internal diseases intensive care unit in Turkey, were analyzed. Therefore, we think that it will contribute to the literature.

In our study, the frequency of gastrointestinal system (GIS) bleeding (19.1%) and acute kidney injury (18.3%) was found to be high in terms of the diagnosis of intensive care hospitalization. This was followed by pneumonia (13%) and sepsis (11.3%). The number of patients hospitalized due to pneumonia, or respiratory failure was less than that of the patients with the non-pulmonary admission diagnosis (n=26 vs. 89). We think that this situation is related to the fact that there are different intensive care units followed by pulmonology specialists in our center.

Furthermore, this study consists of patients followed during the new coronavirus pandemic period. For this reason, a severe acute respiratory syndrome coronavirus-2 polymerase chain reaction (SARS-CoV-2 PCR) test was performed for all patients before hospitalization in the general intensive care unit, as per the health policy, and the patients who were found negative were admitted to our intensive care unit. Patients with positive SARS-CoV-2 PCR tests and needing intensive care were followed up in different intensive care units and were not included in the study.

It has been shown in previous studies that patients hospitalized with a diagnosis of sepsis have a higher mortality rate (20). In our study, the relationship between admission diagnosis and discharge status was evaluated, and it was observed that the patients hospitalized with a diagnosis of sepsis had significantly higher mortality (p=0.001). It has been shown that patients hospitalized due to GIS bleeding have significantly less mortality (p=0.016).

When the severity of all surviving and deceased patients was evaluated according to the prognostic scoring systems, increased values in all APACHE-II, APACHE-IV, SAPS-2, and MPM0 -III scores were associated with increased mortality. This data is also compatible with the literature (1-3,5).

Internal medicine intensive care units differ from general intensive care units with hospitalized patient characteristics. For this reason, we think that our study will contribute to the literature and provide information to clinicians in the regional internal medicine intensive care unit.

However, our study includes the data of patients who were followed up in a single hospital for 6 months. This is the most important limitation of our study. We think that multicenter studies are needed to generalize the findings.

CONCLUSION

Although APACHE-II, APACHE-IV, SAPS-2, and MPM0-III scores are good predictors of mortality, none of these scoring systems is superior to the other for mortality prediction of patients in internal medicine intensive care units..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun Research and Training Hospital Non-interventional Clinical Researches Ethics Committee (Date: 25.08.2021, Decision No: GOKA/2021/15/3).

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. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med 2006; 34: 1297-310.
2. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270: 2957-63.
3. Moreno RP, Metnitz PG, Almeida E, et al. From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med 2005; 31: 1345-55.
4. Metnitz PG, Moreno RP, Almeida E, et al. From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. Intensive Care Med 2005; 31: 1336-44.
5. Higgins TL, Kramer AA, Nathanson BH, Copes W, Stark M, Teres D. Prospective validation of the intensive care unit admission Mortality Probability Model (MPM0-III). Crit Care Med 2009; 37: 1619-23.
6. Castella X, Artigas A, Bion J, Kari A. A comparison of severity of illness scoring systems for intensive care unit patients: results of a multicenter, multinational study. The European/North American Severity Study Group. Crit Care Med 1995; 23: 1327-35.
7. Poole D, Rossi C, Latronico N, Rossi G, Finazzi S, Bertolini G. Comparison between SAPS II and SAPS 3 in predicting hospital mortality in a cohort of 103 Italian ICUs. Is new always better? Intensive Care Med 2012; 38: 1280-8.
8. MD CALC. APACHE II Score-Estimates ICU mortality. Available online: https://www.mdcalc.com/calc/1868/apache-ii-score (accessed Feb 2022)
9. Intensve Cate Network. Available online: https://intensivecarenetwork.com (accessed Feb 2022)
10. ClinCalc. SAPS II Calculator Simplified Acute Physiology Score (SAPS) II calculator to predict hospital mortality. Available online: https://clincalc.com/IcuMortality/SAPSII.aspx (accessed Feb 2022)
11. UpToDate. Calculator: Mortality Probability Admission Model (MPM0-III) for critical illness in adults. Available online: https://www.uptodate.com/contents/calculator-mortality-probability-admission-model-mpm0-iii-for-critical-illness-in-adults (accessed Feb 2022
12. Keegan MT, Gajic O, Afessa B. Severity of illness scoring systems in the intensive care unit. Crit Care Med 2011; 39: 163-9.
13. Freire P, Romãozinho JM, Amaro P, Ferreira M, Sofia C. Prognostic scores in a gastroenterology intensive care unit. Rev Esp Enferm Dig 2010; 102: 596-601.
14. Akavipat P, Thinkhamrop J, Thinkhamrop B, Sriraj W. Acute Physİology And Chronİc Health EvaluatİOn (APACHE) II Score-the clinical predictor in neurosurgıial intensive care unit. Acta Clin Croat 2019; 58: 50-6.
15. Godinjak A, Iglica A, Rama A, et al. Predictive value of SAPS II and APACHE II scoring systems for patient outcome in a medical intensive care unit. Acta Med Acad 2016; 45: 97-103.
16. Gürsoy G, Gürsoy C, Kuşcu Y, Gümüş Demirbilek S. APACHE II or INCNS to predict mortality in traumatic brain injury: A retrospective cohort study. Ulus Travma Acil Cerrahi Derg 2020; 26: 893-8
17. Gai X, Wang Y, Gao D, Ma J, Zhang C, Wang Q. Risk factors for the prognosis of patients with sepsis in intensive care units. PLoS One 2022 6;17: e0273377.
18. Liu C, Suo S, Luo L, Chen X, Ling C, Cao S. SOFA Score in relation to Sepsis: Clinical Implications in Diagnosis, Treatment, and Prognostic Assessment. Comput Math Methods Med 2022 ; 2022: 7870434.
19. Argyriou G, Vrettou CS, Filippatos G, Sainis G, Nanas S, Routsi C. Comparative evaluation of Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scoring systems in patients admitted to the cardiac intensive care unit. J Crit Care 2015; 30: 752-7
20. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006 ; 34: 344-53.

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Neurologic symptoms and signs observed in critical COVID-19 patients may be precursors of existing cerebrovascular disease

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ABSTRACT

Introduction: Although COVID-19 disease often includes respiratory system findings, that affects the gastrointestinal system, circulatory system, coagulation system and neurological system. In this study, we identified the neurological signs and symptoms observed in critical COVID-19 patients.

Material and Method: This retrospective study reviewed 595 COVID-19 patients admitted to our intensive care unit (ICU) between January to June 2020. Patients with neurologic symptoms that were divided into two groups were diagnosed neurological disease (group ND) and non-neurological disease (group non-ND). Clinical signs and symptoms, radiological findings, demographic data (age, gender, presence of comorbidities), white blood cell (WBC), lymphocyte, platelet, lactic acid, glucose, and D-dimer levels, length of hospitalization, requirement of mechanical ventilation, and mortality were recorded for each patient.

Results: Neurologic symptoms were observed in 148 (24.8%) patients. Of these, 44 patients were diagnosed neurological disease and 104 patients were non- neurological disease. The prevalence of neurologic symptoms was significantly higher in group ND. The rate of acute ischemic cerebrovascular disease in 595 critical COVID-19 patients was 6.2%.

Conclusion: Presence of cerebrovascular diseases should be suspected in COVID-19patients with paresis, altered consciousness, numbness, taste/smell disorders, and plegia. The rate of ischemic cerebrovascular disease was approximately seven times higher than the rate of hemorrhagic cerebrovascular disease in critically COVID-19 patients.

Keywords: Intensive care unit, neurology, COVID-19, acute ischemic stroke

This study was presented as an e-poster at the 21st National Intensive Care Congress 17-20 March 2022, Kaya Palazzo Hotel, Antalya.

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) has spread all over the world and has become a pandemic, creating a 'new normal' for almost all nations (1). Although the disease initially showed itself with respiratory tract disease findings, it was observed that it had an effect on the gastrointestinal system, circulatory system, coagulation system and similar systems. Among these conditions, the most common cardiovascular complications, persistent hyperlipidemia, glucose hemostasis irregularities, acute renal failure, acute gastrointestinal effects, acute viral hepatitis, and acute diabetes mellitus have been reported due to its effects on pancreatic islet cells (2). Acute and post-acute neurologic symptoms, signs, and diagnoses of COVID-19 disease have been documented in an increasing number of patients (3). SARS-CoV-2 can invade and damage angiotensin-converting enzyme-2 (ACE2) receptors, and the condition can have neurologic consequences (4). There are studies reporting that systemic hyperinflammation, cerebrovascular events, seizures, and toxic-metabolic encephalopathy caused by a potential SARS-CoV-2 central nervous system infection may cause mental changes in COVID-19 (5).

Neurological symptoms/signs or diagnoses were evaluated in a retrospective cohort study of COVID-19 positive patients. In this study, neurological symptoms were grouped as major and minor symptoms. Encephalopathy, ischemic or hemorrhagic stroke, and seizures were defined as major manifestations, while minor neurological manifestations included headache,

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anosmia, dysgeusia, dizziness or vertigo, and myalgia. The study found that the development of major neurological signs during the course of the disease was an independent predictor of mortality (6).

In this study, we aimed to determine the neurologic signs and symptoms observed in critical COVID-19 patients.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Clinical Researchs Ethics Committee (Date:11/02/2021, Decision No: 2020-KAEK-143-39). All procedures were carried out in accordance with the ethical rulesand the principles of the Declaration of Helsinki.

This retrospective study reviewed 595 COVID-19 patients admitted to XXX hospital intensive care unit (ICU) between January to June 2020. All the patients were classified as critical COVID-19 patients according to the COVID-19 Adult Patient Management Guidelines published by the Ministry of Health (7). Of these, 148 (24.9%) patients were suspected to have neurologic diseases. Data on the signs and symptoms of the patients were retrieved from the clinical notes taken by the physicians that examined the state of consciousness, and the patient anamnesis obtained from the patient or the relatives.

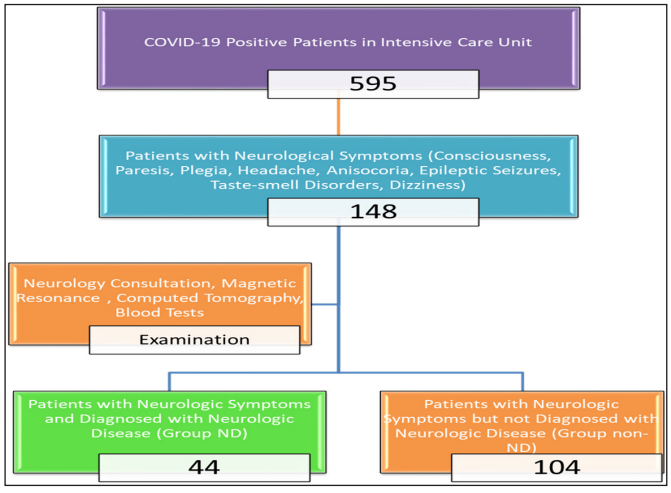

Figure 1: Patient's flow chart

Only patients that were consulted by an experienced neurologist for the assessment of the state of consciousness, paresis, plegia, headache, anisocoria, epileptic seizures, taste-smell disorders, and dizziness were included in the study. Some symptoms of patients were learned from relatives or physicians. When the neurologist consulted, she could not detect the symptoms stated in some of the patients and radiological imaging was not deemed appropriate. Based on the neurologic examination and laboratory and radiological findings, 44 out of 148 patients were diagnosed neurologic disease and these patients were assigned to Group neurological disease (ND). The remaining 104 patients who were not diagnosed with neurologic disease but had neurologic symptoms were assigned to Group non- neurologic disease (non-ND). All the patients had a positive polymerase chain reaction (PCR) test result. Clinical signs and symptoms, radiological findings, demographic data (age, gender, presence of comorbidities), white blood cell (WBC), lymphocyte, platelet, lactic acid, glucose, and D-dimer levels, length of hospitalization, requirement of mechanical ventilation, and mortality were recorded for each patient.

Statistical Analysis

Data were analysed using SPSS for Windows version 22 (Armonk, NY: IBM Corp.). Normal distribution of continuous variables was assessed using One-Sample Kolmogorov-Smirnov test. Variables with normal distribution were compared using Independent-Samples t-test and variables with non-normal distribution were compared using Mann-Whitney U test. Categorical variables were compared using Pearson Chi-square and Fisher Exact tests. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as frequencies (n) and percentages (%). A p value of <0.05 was considered significant. Data were defined as median (1st quartile-3rd quartile) for non-normal continuous variables and frequency (percent) for categorical variables.

RESULTS

Neurologic symptoms were detected in 148 of 595 critical COVID-19 patients. Of these 148 patients, 44 patients were diagnosed with neurological disease as ischemic cerebrovascular disease, hemorrhagic cerebrovascular disease and Guillain-Barre Syndrome (GBS) (Group ND) and 104 were non-neurological disease (Group non-ND). 90 of 148 patients had radiological imaging. Diagnostic imaging could not be performed on other patients because their clinical conditions were not suitable for transfer. In group ND, only cranial computed tomography (CT) was performed in 1, only magnetic resonance imaging (MRI) was performed in 26, and both CT and MRI were performed in 17 patients. In group non- ND, CT was performed in 15, MRI was performed in 18, and both CT and MRI were performed in 13 patients.

Group ND consisted of 26/44 (59.1%) male and 18/44 (40.9%) female and group non-ND consisted of 76/104 (73.1%) male and 28/104 (26.9%) female. Mean age was significantly higher in Group ND than in Group non-ND (71.1±13.6 vs. 65.64±13.4 years) (p=0.002).

No significant difference was observed between the two groups with regard to the presence of comorbidities, requirement of mechanical ventilation, and length of ICU stay. Mortality occurred in 19 (43.2%) patients in Group ND and in 63 (60.6%) patients in Group non-ND (p=0.052) (**Table 1**).

Table 1: Demographic data of the patients

Demographic data	Group ND (n: 44)	Group non-ND (n: 104)	P
Female	18 (40.9%)	28 (26.9%)	0.093[a]
Male	26 (59.1%)	76 (73.1%)	0.093[a]
Age (Mean + SD)	71.1 (+ 13.6)	65.64(+13.4)	*0,002[b]
Additional disease presence			
Diabetes mellitus	10 (22.7%)	22 (21.2%)	0.832
Hypertension	17 (38.6%)	38(36.5%)	0.809[a]
Cardiovascular disease	15 (34.1%)	31 (29.8%)	0.607[a]
Other (malignant, hematological patient etc.)	31 (70.5%)	62(59.6%)	0,212[a]
Need for mechanical ventilator	29 (65.9%)	77 (74.0%)	0,316[a]
Number of ICU treatment days (Mean + SD)	11.55 (+7.3)	14,03 (+12.8)	0,231[b]
Mortality	19 (43.2%)	63 (60.6%)	0.052[a]

All data are expressed as mean ± standard deviation (SD), as percent (%) or as numbers. [a]Chi-Square Test. [b]Independent Samples T-Test.*p<0.05

Both WBC and lymphocyte values were significantly higher in group ND. In contrast, C-reactive protein (CRP) and ferritin levels were found to be significantly higher in group non – ND. Although glucose levels were higher in group non- ND, no significant difference was observed (**Table 2**).

Table 2: Laboratory data of the patients

	Group ND (n: 44) (Mean+SD)	Group non- ND (n:104) (Mean+SD	p
White blood cell	9.42+3.89	7.79+4.39	*0.012[a]
Lenfosit	1.17+0.58	0.98+0.60	*0.035[a]
Platelet count	203.64+92.63	198.56+95.87	0.76[b]
D dimer	2.41+2.65	2.78+3.20	0.33[a]
C-reactive protein	79.41+64.17	131,31+79.12 (1-412)	*<0.001[a]
Lactate	2.96+1.86	2.66+1.45	0.46[a]
Glucose	175.16+73.68	271.27+72.17	0.78[a]
Ferritin	330.01+302.62	636.43+457.41 (5-1500)	*<0.001[a]

All data are expressed as mean ± standard deviation (SD) or as numbers.a İndependent Samples T-Test.b Mann-Whitney U Test *p<0.05

Numbness was the most common neurologic symptom (70/595, 13.4%), followed by altered consciousness (39/595, 6.5%), dizziness (39/595, 6.5%), paresis (35/595, 5.8%), headache (34/595, 5.6%), taste disorder (35/595, 5.8%), smell disorder (35/595, 5.8%), plegia (26/595, 4.3%), epileptic seizure (22/595, 3.6%), and anisocoria (13/595, 2.1%). The prevalence of neurologic symptoms was significantly higher in Group ND. While the anisocoria observed in Group non- ND patients are accepted as physiological or error evaluation by the neurologist, the anisocoria observed in Group ND are the patients with hemorrhagic cerebrovascular disease or stroke (**Table 3**).

Table 3: Distribution of neurologic symptoms and signs in critical COVID-19 patients

Neurologic Symptoms And Signs	Group ND 44 (%)	Group non – ND 104 (%)	All COVID-19 Patients in ICU 595 (%)
Change of Consciousness	29 (65.9%)	10 (9.6%)	39 (6.5%)
Headache	19 (43.1%)	15 (14.4%)	34 (5.6%)
Dizziness	18 (40.9%)	21 (20.1%)	39 (6.5%)
Plegia	25 (56.8%)	1 (0,96%)	26 (4.3%)
Paresis	32 (72.7%)	3 (2.8%)	35 (5.8%)
Anisocoria	9 (20.4%)	4 (3.8%)	13 (2.1%)
Taste Disorder	27 (61.3%)	8 (7.6%)	35 (5.8%)
Smell Disorder	25 (58.8%)	10 (9.6%)	35 (5.8%)
Epileptic Seizure	20 (45.4%)	2 (1.9%)	22 (3.6%)
Numbness	28 (63.6%)	42 (40.3%)	70 (13.4%)

All data are expressed as numbers and as percent (%)

Of the 595 critically ill patients, 44 were diagnosed with neurologic disease. 37/595 (6.2%) had ischemic cerebrovascular disease, 5/595 (0.8%) had hemorrhagic cerebrovascular disease, 2/595 (0.3%) had Guillain-Barre Syndrome (GBS).

DISCUSSION

In this study, neurological symptoms were observed in 148 of 595 admitted to our COVID-19 intensive care unit. Forty-four of 148 patients were diagnosed with neurological disease. While both lymphocyte and WBC levels were higher in patients diagnosed with neurological disease, CRP and ferritin levels were significantly higher in patients with neurological symptoms but not diagnosed with neurological disease. On the other hand, the prevalence of neurological symptoms was higher in patients diagnosed with neurological disease. In addition, although mortality was higher in patients without a diagnosis of neurological disease than in patients with a diagnosis of neurological disease, no significant difference was observed between them.

The mean age of patients diagnosed with neurological disease was found to be significantly higher than patients without a diagnosis of neurological disease, and in accordance with the literature, the number of male patients was higher than females in both groups (8,9,10).

Admission of patients to the intensive care unit is decided by evaluating severe respiratory distress, hemodynamic instability, changes in consciousness and serious changes in laboratory evaluation. In the case of all patients with

COVID-19, the high lymphocyte and neutrophil values of the patients in the ND group led us to think that these patients needed intensive care not because of the severity of the COVID-19 disease, but because of the severity of their underlying neurological condition. Among the prognostic factors of COVID-19 disease are low lymphocyte, high ferritin and high CRP. In this context, the low lymphocyte high CRP and ferritin values in patients in the non-ND group can also be explained for the same reason. A meta-analysis evaluating 83 studies reports that inflammatory markers such as ferritin and neutrophil-lymphocyte ratio have a significant relationship with mortality in COVID-19 patients (11). Another study reported that lymphocyte and platelet levels were lower in COVID-19 patients with central nervous system (CNS) involvement compared to those without (12). However this study was not conducted in intensive care patients.

In our study, paresis, altered consciousness, and numbness were associated with a higher prevalence of cerebrovascular diseases. Although the effect of COVID-19 on CNS remains unclear, there are several theories to explain it. The first theory is that the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) causes endotheliitis in COVID-19 disease, thereby invading CNS through a hematogenous route. The second is that SARS-CoV-2 initially causes peripheral neuritis and then invades CNS via retrograde axonal transport from peripheral nerves (13). The third theory is that SARS-CoV-2 accesses CNS through the olfactory bulb, thereby causing neurodegeneration (14). The fourth theory is that SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) in brain endothelial and smooth muscle cells, followed by depletion of ACE2 by SARS-CoV-2, resulting in an elevation in Angiotensin II that increases the risk of proinflammatory, vasoconstrictive, and organ damage. In addition, it has also been hypothesized that clinical conditions causing tissue damage (e.g. stroke) occur due to an increase in Angiotensin II. Based on the fourth theory, Hess et al. (15) found a relationship between COVID-19 and stroke.

Mao et al. (16) detected neurologic symptoms in 78 (36.4%) out of 214 COVID-19 patients . Similarly, Helms et al. (17). observed neurologic symptoms in 84% of patients with severe SARS-CoV-2 infection requiring intensive care, with the most common symptoms including encephalopathy, agitation, and confusion. In our study, neurologic symptoms were detected in 148 (24.8%) out of 595 COVID-19 patients.

Literature indicates a wide range of prevalence for neurologic symptoms in COVID-19 patients. In our study, the rate of altered consciousness in COVID-19 patients was 9% (18). In a study conducted with COVID-19 patients in Wuhan, headache was observed in 8% and confusion/confusion was detected in 9% of the patients (19). Amanat et al. (20) evaluated neurologic symptoms accompanying COVID-19 in 873 patients and reported that the most common neurologic symptoms included myalgia (24.8%), headache (12.6%), and dizziness (11.9%). There are some studies suggesting that symptoms such as smell and taste disorders may be among the early signs of COVID-19 (21). In a systematic meta-analysis, Whittaker et al. (22) evaluated 31 studies investigating neurologic symptoms of COVID-19 patients and reported that the most common symptoms included headache (6-45%), dizziness (7-17%), altered consciousness (8%), taste disorders (6-89%), smell disorders (5-86%), and epileptic seizures (0.5%) (21).

In a large cohort study, Yaghi et al. (23) diagnosed ischemic stroke in 32 (0.9%) out of 3556 patients hospitalized with a diagnosis of COVID-19 infection. However, unlike our study, the study included non-critical COVID-19 patients. Toscano et al. (24) reported on five patients with GBS from three hospitals in northern Italy during the COVID-19 outbreak. In the study by Amanat et al. (25) 10 out of 873 COVID-19 patients had cerebrovascular diseases, one patient had status epilepticus, one patient had demyelinating disease, and one patient was diagnosed with Guillain-Barre Syndrome (GBS).

An epileptic seizure is a transient event with signs or symptoms due to abnormal excessive and synchronous neuronal activity in the brain. If it is thought to be a seizure, it should be examined whether it was provoked or unprovoked. In order to distinguish whether there is a seizure triggered by the COVID-19 disease, blood tests and lumbar puncture are applied to the patient. SARS-CoV2 features neurotropism (26). The prognosis of patients with seizures mostly depends on any underlying cause. Patients with seizures due to curative medical or toxicological causes should manage these problems well. One epilepsy patient in our non-ND group did not have any seizures afterward, and lumbar puncture could not be performed due to the use of antiaggregant and anticoagulation. The plegic patient in the non-ND group unfortunately died before the necessary examinations were completed.

Neural invasion by the virus, difficulty in blood pressure regulation, a systemic hyperinflammatory state characterized by hypercytokinemia, and thrombocytopenia are theories that can explain intracranial hemorrhages in COVID -19 patients. COVID-19 associated coagulopathy (CAC) may be a good explanation for ischemic cerebrovascular diseases. Mechanisms such as inflammation, endothelith, hyperviscosity and hypercoagulation lead to a high thrombotic risk in patients with COVID-19. If we look at

the studies of Hernández–Fernández (27) and Meppiel (28), considering the published cases of intracranial hemorrhage in COVID-19 patients, the majority of them are multi-lobular in nature and mortality is reported at a rate of 47%. Cerebral hemorrhages observed in COVID-19 patients are thought to be possibly related to COVID-19 coagulopathy (29). In our study, ICH was only noticed in patients with severe COVID-19 disease.

Among postmortem studies, a study by Li et al.(25) evaluated viral neuroinvasion of SARS-CoV-2 via cerebrospinal fluid testing and brain autopsies and found that the detection rate of SARS-CoV-2 was higher in the olfactory system and brain stem, both of which had severe microgliosis and lymphocytic infiltrations, unlike in the cerebrum and cerebellum. Accordingly, it can be asserted that there are some other neurologic diseases that have not yet been defined in COVID-19. In their study, Eray et al. (30) showed that various neuropsychiatric complications may be an important part of the long-term effects of COVID-19. These diseases can be in the form of inflammatory encephalitis or peripheral neuritis. However, the criticality of the patients' condition, presence of bleeding and coagulation problems, and the requirement of follow-up with neuromuscular blockers may prevent the implementation of cerebrospinal fluid testing or electromyography procedures. Although symptomatic patients do not have a neurologic diagnosis, the higher inflammatory markers in non-ND group indicate the presence of viral sepsis.

Due to the simultaneous admission of multiple COVID-19 patients to hospitals during the pandemic period, the use of diagnostic techniques including MRI, cerebrospinal fluid testing, and electromyography was avoided due to increased risk of cross-infection and bleeding. Therefore, only subjective symptoms of our patients were evaluated in the study. Another limitation of this study was the evaluation of patients at first admission to ICU. The initial acceptance of most of the patients was the COVID-19 reporting and data system values of 2-3, and the thoracic tomography evaluations of the worsening periods were not evaluated.

CONCLUSION

Presence of neurologic diseases should be suspected in COVID-19 patients with paresis, altered consciousness, numbness, taste/smell disorders, and plegia. COVID-19 is a disease with bleeding coagulation disorder and the rate of ischemic cerebrovascular disease is approximately seven times higher than the rate of haemorrhagic cerebrovascular disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Researchs Ethics Committee (Date:11/02/2021, Decision No: 2020-KAEK-143-39).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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REFERENCES

1. Mishra SK, Tripathi T. One year update on the COVID-19 pandemic: where are we now? Acta Trop 2021; 214: 105778.
2. Akbarialiabad H, Taghrir MH, Abdollahi A, et al. Long COVID, a comprehensive systematic scoping review. Infection 2021; 49: 1163-86.
3. Beghi E, Giussani G, Westenberg E, et al. Acute and postacute neurological manifestations of COVID-19: present findings, critical appraisal, and future directions. J Neurol 2022; 269: 2265-74.
4. Wenting A, Gruters A, van Os Y, et al. COVID-19 neurological manifestations and underlying mechanisms: a scoping review. Front Psychiatry 2020; 11: 860.
5. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology 2020; 296: 0–20.
6. Salahuddin H, Afreen E, Sheikh IS, et al. Neurological predictors of clinical outcomes in hospitalized patients with COVID-19. Front Neurol 2020; 11: 585944.
7. Republic of Turkey Ministry of Health; Https://COVID19.Saglik.gov.tr/Eklenti/40719/0/COVID-19rehberieriskinhastayonetimivetedavipdf.pdf Access Date: 07 May 2021.
8. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-Cov-2 admitted to icus of the Lombardy region, Italy. JAMA 2020; 32: 1574-81.
9. Kokoszka-Bargieł I, Cyprys P, Rutkowska K, et al. Intensive care unit admissions during the first 3 months of the COVID-19 pandemic in Poland: a single-center, cross-sectional study. Med Sci Monit 2020; 26: E926974.
10. Xudong X, Junzhu C, Xingxiang W, et al. Age- and gender-related difference of ACE2 expression in rat lung. Life Sci 2006; 78: 2166–71.
11. Mahat RK, Panda S, Rathore V, et al. The dynamics of inflammatory markers in coronavirus disease-2019 (COVID-19) patients: a systematic review and meta-analysis. Clin Epidemiol Glob Health 2021; 11: 100727.
12. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020; 5: 279-84.

13. Desforges M, Le Coupanec A, Dubeau P, et al. Coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system?. Viruses 2019; 12: 14.
14. Fodoulian L, Tuberosa J, Rossier D, et al. SARS-Cov-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium and brain. iScience 2020; 18: 101839.
15. Hess DC, Eldahshan W, Rutkowski E. COVID-19-Related Stroke. Transl Strok Res 2020; 11: 322–5.
16. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77: 683-90.
17. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-Cov-2 infection. N Engl J Med 2020; 382: 2268-70.
18. Li Y, Wang M, Zhou Y. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020; 5: 279-84.
19. 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.
20. Amanat M, Rezaei N, Roozbeh M, et al. Neurologic manifestations as the predictors of severity and mortality in hospitalized individuals with COVID-19: a multicenter prospective clinical study. BMC Neurol 2021; 21: 116.
21. Chang CC, Yang MH, Chang SM, et al. Clinical significance of olfactory dysfunction in patients of COVID-19. J Chin Med Assoc 2021; 84: 682-9.
22. Whittaker A, Anson M, Harky A. Neurologic manifestations Of COVID-19: a systematic review and current update. Acta Neurol Scand 2020; 142: 14–22.
23. Yaghi S, Ishida K, Torres J, et al. SARS-Cov-2 and stroke in a New York Healthcare System. Stroke 2020; 51: 2002–11.
24. Toscano G, Palmerini F, Ravaglia S Guillain-Barré syndrome associated with SARS-Cov-2. N Engl J Med 2020; 382: 2574-6.
25. Li YC, Zhang Y, Tan BH. What can cerebrospinal fluid testing and brain autopsies tell us about viral neuroinvasion of SARS-Cov-2. Med Virol 2021; 9: 4247-57.
26. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014; 55: 475-82.
27. Hernández-Fernández F, Valencia HS, Barbella-Aponte R. A cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. Brain 2020; 143: 3089–103
28. Meppiel E, Peiffer-Smadja N, Maury A. Neurologic manifestations associated with COVID-19: a multicentre registry. Clin Microbiol Infect 2021; 27: 458-66.
29. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844–7.
30. Eray U, Ayrıbaş B, Çağlar ÖF, Hacıoğlu T, Alibeyoğlu F. Post-COVID syndrome? COVID-19survivors suffer from cognitive difficulties, somatic complaints and anxiety. J Health Sci Med 2022; 5: 1328-33.

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Choroidal thickness and retinal nerve fiber layer analysis in chronic spontaneous urticaria

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ABSTRACT

Aim: In this study, we investigated the effects of chronic spontaneous urticaria on the choroid and retinal nerve fiber layer.

Material and Method: The patient group consisted of newly diagnosed 54 chronic spontaneous urticaria (CSU) patient and the control group consisted of 54 healthy volunteer. Choroidal and retinal nerve fiber layer (RNFL) thickness measurements were performed with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) 30 minutes after pupil dilation with 0,5% tropicamide.

Results: In the patient group, nasal choroidal thickness (NCT) was 290.11±43.16 µm, subfoveal choroidal thickness (SFCT) was 339.17±37.709 µm, temporal choroidal thickness (TCT) was 296.00±42.859 µm, mean choroidal thickness (MCT) was 308.33±35.923 µm and RNFL thickness was 91.11±7.393 µm. NCT was 248.42±35,742 µm, SFCT 276.56±40.04 µm, TCT 253.69±37.384 µm, MCT 259.50±32,986 µm and RNFL thickness 92.19±8.719 µm in the control group. When we examine the p value, it is seen that both groups are similar to each other in terms of RNFL thickness (p=0.326), while there is a significant thickening in all choroidal regions of patients with CSU, including NCT, SFCT, TCT, MCT (p=0.000, p=0.000, p=0.000, p=0.000, respectively).

Conclusion: The choroid is affected in CSU and choroidal thickness can be a noninvasive method that can be used in diagnosis CSU. However, studies of longer disease durations may provide more illuminating information about CSU and choroid and RNFL.

Keywords: Choroidal thickness, chronic spontaneous urticaria, EDI-OCT, histamine, retinal nerve fiber layer

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a skin disease that lasts for at least 6 weeks and is characterized by itching and swelling without a triggering factor (1). Although the exact etiopathogenesis of the disease has not been determined yet, there is perivascular infiltration of inflammatory cells at the lesion site in CSU and blebs are known to contain prostaglandins and leukotrienes, platelet-activating factors, histamine, cytokines and proteases released by degranulation of skin mast cells (2). As these inflammatory mediators increase vascular permeability, redness, itching and edema occur (3).

The choroid is a network of vessels that serves as nutrition for the fovea, outer retina and optic nerve. The choroid contains dense plexuses of nerve fibers controlled by the autonomic nervous system (4). Parasympathetic and sympathetic nervous system activation and the inflammation can produce changes in the choroidal circulation and thus changes in thickness. With the new generation of advanced deep imaging optical coherence tomography (EDI-OCT) devices, the choroid can now be visualized and choroidal thickness and thickness changes can be measured. For this reason, changes in choroidal thickness have been the subject of many studies in recent years, and the effects of various systemic diseases on choroidal thickness have been studied (5). Choroidal thickness examinations were performed on the diseases with skin involvement such as vitiligo, rosacea, and Behçet's disease (6-8).

New generation OCT devices can detect changes in the retinal nerve fiber layer (RNFL) by performing retinal nerve fiber analysis. RNFL thickness changes, which are generally used in the diagnosis and follow-up of glaucoma, have been studied in many retinal

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and systemic diseases (8-10). RNFL analysis has been evaluated in inflammatory diseases with skin involvement such as Vogt Koyanagi Harada and vitiligo (11,12). As far as we know, no retina examination has been done in CSU. Since retinal dysfunction has been reported in patients with an inflammatory disease such as vitiligo, we wanted to analyze RNLF in CSU (12). At the same time, the inflammatory process in CSU can cause an increase in ganglion cell apoptosis. We think that inflammation caused by inflammatory cell infiltration and inflammatory mediator release in CSU may affect the choroidal thickness and RNFL. Therefore, in our study, we examined the choroidal thickness and RNFL analysis of our CSU patients who have not yet been treated.

MATERIAL AND METHOD

This study was carried out by dermatology and ophthalmology departments as cross-sectional. The study was carried out with the permission of Niğde Ömer Halisdemir University Noninvasive Clinical Researches Ethics Committee (Date: 26.05.2022 Decision No: 2022/69). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Oral and written consent was obtained from each patient before the eye examination.

The study group was formed by determining patients who were diagnosed with CSU by the dermatology department of our hospital and have not been treated yet. Fifty-four CSU patients without any eye disease or complaint and 54 healthy individuals as a control group were included in the study. The patient and control groups consisted of volunteers with 10/10 vision according to the Snellen chart and no eye pathology except refractive error. The axial lengths of our participants were between 22-24mm. In both groups; patients older than 18 years of age were included in the study, those with systemic disease other than CSU, pregnancy and lactation, myopia and hyperopia greater than 3D, astigmatism greater than 2D, and those with a history of ocular surgery were excluded from the study. At the same time participants with smoking and alcohol use were excluded. Body max index of our participants was between 18.5-24.9.

Demographic information of all cases were recorded. All individuals were questioned about their detailed medical history. A full ophthalmoscopic examination including best corrected visual acuity, eye pressure measurement with a pneumatic tonometer (corrected according to pachymeter), color vision, light reflexes, eye movements, anterior and posterior segment examination with slit lamp slit lamp was performed. Both eyes of all participants were included in the study.

Choroidal thickness measurement and RNFL analysis with Optical Coherence Tomography Examination

Measurements were made with Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) 30 minutes after administration of 0,5% tropicamide. Measurements with a signal quality of 6 and above in both choroidal thickness and RNFL analysis were included in the study.

Choroidal thickness was measured with the device's single line HD 5 Line Raster protocol and depth imaging system (EDI) mode. The first measurement was subfoveal choroidal thickness (SFCT). The thickness was found by measuring the distance between the retinal pigment epithelium (RPE) hyperreflective band and the choroido-scleral junction. Then, measurements were made from 6 points in the temporal and nasal directions from the subfoveal region at 500 micron intervals and up to 1500 microns, 3 temporally (TCT) and 3 nasally (NCT). Mean choroidal thickness (MCT) was calculated by taking the average of the measurements from 7 points.

For RNFL measurement, three-dimensional (3D) cube OCT data were obtained using the optic nerve head-centered "Optical Disc Cube 200 X 200 Scan" model. After the RNFL map formed, the RNFL thickness is determined by an automatic computer algorithm.

Statistical Analysis

Statistical analyzes were performed using the STATA 14 package program. In the descriptive table, numerical variables were summarized with mean±standard deviation [minimum – maximum] values, and categorical variables were shown as numbers and percentages. The Kolmogorov-Smirnov test was used to evaluate normal distribution, and the homogeneity of the variances was examined with the Levene test. Significance level was taken as $p<0.05$.

RESULTS

The patient group consisted of 108 eyes, 72 female and 36 male eyes, and the mean age of the group was 43.06±14.007. In the control group, 66 eyes were female and 42 were male of 108 eyes, and the mean age of the group was 43.94±13,593. Differences between the patient and control groups were examined in **Table 1** and it was found that the two groups were similar to each other in terms of age and gender (p=.0.636 and p=0.395 respectively).

Table 1: Age and gender distribution

	Chronic spontaneous urticaria group n: 108	Control group n:108	p
Age	43.06±14.007	43.94±13.593	0.636
Gender			0.395
Female N (%)	72 (66.7%)	66 (61.1%)	
Male N (%)	36 (33.3%)	42 (38.9%)	

In **Table 2**, NCT, SFCT, TCT, MCT and RNFL values were compared between patients with CSU and the control group. In the patient group, NCT was 290.11±43.16 µm, SFCT was 339.17±37.709 µm, TCT was 296.00±42.859 µm, MCT was 308.33±35.923 µm and RNFL thickness was 91.11±7.393 µm. NCT was 248.42±35,742 µm, SFCT 276.56±40.04 µm, TCT 253.69±37.384 µm, MCT 259.50±32,986 µm and RNFL thickness 92.19±8.719 µm in the control group. When we examine the p value, it is seen that both groups are similar to each other in terms of RNFL thickness (p=0.326), while there is a significant thickening in all choroidal regions of patients with CSU, including NCT, SFCT, TCT, MCT (p=0.000, p=0.000, p=0.000, p=0.000, respectively).

Table 2. Comparison of choroidal and RNFL thicknesses between groups

	CSU group (n=108)	Control group (n=108)	p
Subfoveal Choroidal Thickness (µm)	339.17±37.709	276.56±40.04	0.000
Nasal Choroidal Thickness (µm)	290.11±43.16	248.42±35.742	0.000
Temporal Choroidal Thickness (µm)	296.00±42.859	253.69±37.384	0.000
Mean Choroidal Thickness (µm)	308.33±35.923	259.50±32.986	0.000
RNFL Thickness (µm)	91.11±7.393	92.19±8.719	0.326

DISCUSSION

Although the etiology of CSU is not known exactly, it has been recently revealed that mechanisms such as immunological, inflammatory and coagulation play a role in its pathogenesis (13). As far as we know, our study is the first to examine the effects of this state of inflammation on the choroid and RNFL in patients with CSU. In our study, we found the choroids of CSU patients to be significantly thicker than the control group, but we did not observe any effect on RNFL thickness.

In the studies conducted in recent years, it is observed that a systemic proinflammatory state is dominant in CSU. It has been reported that adiponectin levels are lower in patients with chronic urticaria, and the levels of molecules such as IL-10, IL-6 and TNF-alpha have increased (14). In addition, autoimmunity plays a role in the pathogenesis and high-affinity IgE receptor-specific IgG antibodies have been found in CSU patients. These autoantibodies contribute to inflammation by activating the complement system, mast cells in the skin, and circulating basophils (15). In the pathogenesis of CSU, pathologies have also been found in the coagulation system. Studies have reported that the coagulation cascade is activated in the patients with CSU, and thus an increase in vascular permeability occurs with the effect of thrombin (16). Activation of the coagulation cascade has also been reported in the skin diseases characterized by increased vascular permeability, such as bullous pemphigoid characterized by increased vascular permeability and angioedema due to C1-inhibitor deficiency (13). It has also been a matter of curiosity whether these existing pathologies are only characterized by the skin. It has been reported that systemic effects due to increased plasma histamine levels in patients with CSU can also be observed (17). Headache, increased gastric acid secretion, tachycardia, decreased arterial pressure, and bronchospasm has been reported as other systemic findings that may occur in CSU (18). Weigert et al. (19) reported that intravenous histamine injection caused an increase in human choroidal blood flow and retinal vessel diameters. In our study, the choroidal thickness of the patients with CSU was found to be thicker than healthy individuals. As far as we know, there is no other study examining choroidal thickness in CSU, so we could not compare our results, but choroidal thickness was examined in various skin diseases. Demirkan et al. (6) reported that the choroidal thickness was thinned in vitiligo patients. Şahin et al. (7) found no change in choroidal thickness in their study of rosacea patients. In addition, the literature has demonstrated that the choroid of patients has been thickened in the active phases of inflammatory diseases with vascular involvement such as lupus and Behçet's disease (20).

The relationship between urticaria and the neurological system has also been investigated in the literature. Wang et al. (21) investigated the functional and structural changes of the striatum in 40 CSU patients and 40 healthy controls and demonstrated striatum dysfunction in CSU. Fumal et al. (22) reported a migraine attack that was presumed to be associated with the systemic release of vasoactive substances such as histamine. Harada et al. (23) presented a case of a 10-year-old boy with cholinergic urticaria associated with epileptic seizures. The neuroectoderm-derived retina, which is an extension of the brain, is also likely to be affected in CSU, but there is no study yet on this subject. Örnek et al. (11) examined RNFL thickness in vitiligo patients and found no difference in RNFL thickness, similar to our study. In our study, we found that the RNFL thickness of the patients with CSU was thinner than healthy controls, but there was no significant difference. We found an increase in choroidal thickness in our study but the absence of any change in RNFL may be due to the difference in the amount of histamine in the tissues. In their tissue study conducted with the eyes that were enucleated secondary to various causes, Nowak et al. (24) reported that the lowest amount of histamine was in the optic nerve and retina and the highest amount of histamine was in the choroid and sclera. Rogosic et al. (25), in a study conducted about vitiligo, it was suggested that there may

be a possible relationship between the duration of vitiligo and glaucoma. They reported that this may be a glaucoma secondary to steroid therapy. Steroids used to treat CSU are likely to affect RNLF. However, patients who have not yet received treatment were examined in our study. This may be why no change has been tracked in the RNFL.

A limitation of the study was the manual measurement of choroidal thickness due to OCT device capability. Therefore, in our study, measurements were made and compared by two independent researchers to check the reliability.

CONCLUSION

The choroid is affected in CSU and choroidal thickness may be a noninvasive method that can be used in diagnosis and treatment follow-up in CSU. However, data on longer disease durations may provide more illuminating information about CSU and choroid and RNFL.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Niğde Ömer Halisdemir University Noninvasive Clinical Ethics Committee (Date:26.05.2022 Decision No: 2022/69).

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. Alizadeh Aghdam M, van den Elzen M, van Os-Medendorp H, et al. Systemic and local evidence for complement involvement in chronic spontaneous urticaria. Clin Transl Allergy 2021; 11: 2011.
2. Saini SS, Kaplan AP. Chronic Spontaneous Urticaria: The Devil's Itch. J Allergy Clin Immunol Pract 2018; 6: 1097-6.
3. Kaplan AP, Horáková Z, Katz SI. Assessment of tissue fluid histamine levels in patients with urticaria. J Allergy Clin Immunol 1978; 61: 350-4.
4. Nickla DL, Wallman J. The multifunctional choroid. Prog Retin Eye Res 2010; 29: 144-68.
5. Steiner M, Esteban-Ortega MDM, Muñoz-Fernández S. Choroidal and retinal thickness in systemic autoimmune and inflammatory diseases: A review. Surv Ophthalmol 2019; 64: 757-69.
6. Demirkan S, Onaran Z, Samav G, et al. Decreased choroidal thickness in vitiligo patients. BMC Ophthalmol 2018; 18: 126.
7. Şahin T, Öztekin A, Cevher S. Does Rosacea, a localized skin disease, affect the choroidal thickness? J Cosmet Dermatol 2022; 21: 387-1.
8. Ataş M, Yuvacı I, Demircan S, et al. Evaluation of the macular, peripapillary nerve fiber layer and choroid thickness changes in Behçet's disease with spectral-domain OCT. J Ophthalmol 2014; 2014: 865394.
9. Lim HB, Sung JY, Ahn SI, Jo YJ, Kim JY. Retinal nerve fiber layer thickness in various retinal diseases. Optom Vis Sci 2018; 95: 247-5.
10. Yılmaz M, Polat OA, Karayiğit DZ, Ayyıldız T. Choroidal vascularity index and choroidal thickness changes in patients with allergic asthma. Photodiagnosis Photodyn Ther 2021; 36:102494.
11. Ornek N, Onaran Z, Koçak M, Ornek K. Retinal nerve fiber layer thickness in vitiligo patients. J Res Med Sci 2013; 18: 405-7.
12. Chee SP, Afrin M, Tumulak MJ, Siak J. Role of optical coherence tomography in the prognosis of Vogt-Koyanagi-Harada disease. Ocul Immunol Inflamm 2021; 29: 118-3.
13. Asero R, Tedeschi A, Marzano AV, Cugno M. Chronic urticaria: a focus on pathogenesis. F1000Res 2017; 6: 1095.
14. Trinh HK, Pham DL, Ban GY, Lee HY, Park HS, Ye YM. Altered systemic adipokines in patients with chronic urticaria. Int Arch Allergy Immunol 2016; 171: 102-10.
15. Fraser K, Robertson L.Chronic urticaria and autoimmunity. Skin Therapy Lett 2013; 18: 5-9.
16. Asero R, Tedeschi A, Riboldi P, Cugno M. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. J Allergy Clin Immunol 2006; 117: 1113-7.
17. Kocatürk E, Grattan C. Is chronic urticaria more than skin deep? Clin Transl Allergy 2019; 9: 48.
18. Son JH, Chung BY, Kim HO, Park CW. A histamine-free diet is helpful for treatment of adult patients with chronic spontaneous urticaria. Ann Dermatol 2018; 30: 164-2.
19. Weigert G, Zawinka C, Resch H, Schmetterer L, Garhöfer G. Intravenous administration of diphenhydramine reduces histamine-induced vasodilator effects in the retina and choroid. Invest Ophthalmol Vis Sci 2006; 47: 1096-100.
20. Steiner M, Esteban-Ortega MDM, Muñoz-Fernández S. Choroidal and retinal thickness in systemic autoimmune and inflammatory diseases: A review. Surv Ophthalmol 2019; 64: 757-69.
21. Wang Y, Fang JL, Cui B, et al. The functional and structural alterations of the striatum in chronic spontaneous urticaria. Sci Rep 2018; 8: 1725.
22. Fumal A, Crémers J, Ambrosini A, Grand JL, Schoenen J. Migraine with urticaria. Neurology 2006; 67: 682.
23. Harada T, Yamamura Y, Ishizaki F, et al. A case of cholinergic urticaria with epileptic seizure and abnormalities on electroencephalogram. No To Shinkei 2001; 53: 863–8.
24. Nowak JZ, Nawrocki J. Histamine in the human eye. Ophthalmic Res 1987; 19: 72-5.
25. Rogosić V, Bojić L, Puizina-Ivić N, et al. Vitiligo and glaucoma - an association or a coincidence? A pilot study. Acta Dermatovenerol Croat. 2010; 18: 21-6.

Original Article

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Investigation of the effects of different nanoparticle additionals on the mechanical properties of silicone elastomer used in maxillofacial prosthesis

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ABSTRACT

Objective: The aim of this study is to evaluate the change in the mechanical properties of silicone elastomer used in the production of maxillofacial prostheses with the addition of 3 different nanoparticles (TiO_2-SiO_2-ZnO).

Material and Method: TiO_2-SiO_2-ZnO nanoparticles were added to the A part of the M511 Platinum (Technovent Ltd., England) silicone elastomer at a rate of 2% by weight. Test specimens were produced in sizes by ASTM D412 standards for tensile strength and percent elongation, ASTM D624 for tear strength, and ASTM D2240-68 for hardness testing. For each mechanical test, 4 groups were formed together with the control group and 3 other groups to which nanoparticles were added, and a total of 132 samples were produced, 11 samples for each group (n=11), (N=132). The data of tensile strength, elongation percentage, and tear strength tests were analyzed by Shapiro Wilk's and/or Kolmogorov Smirnov/Mann Whitney U, Kruskal Wallis-H tests; for the hardness test, the values in each group showed a normal distribution within themselves, hardness test was analyzed with Oneway ANOVA/Tukey HSD tests.

Results: The addition of TiO_2 and SiO_2 to the silicone elastomer significantly increased the tensile strength compared to the other groups ($p<0.05$), the addition of TiO_2 increased the elongation percentage significantly compared to the other groups ($p<0.05$), all particle additions significantly increased the tear strength ($p<0.05$), SiO_2 addition significantly increased the hardness compared to the other groups.

Conclusion: The addition of TiO_2-SiO_2-ZnO nanoparticles to silicone elastomer may be an effective option to improve the mechanical properties of maxillofacial prostheses.

Keywords: Maxillofacial prostheses, nanoparticles, silicone elastomer

INTRODUCTION

Defects may occur in the maxillofacial region as a result of congenital, developmental or acquired causes (1). Congenital malformations in the maxillofacial region, and facial deformities that may occur due to head and neck surgery or trauma cause psychological problems and alienation of patients from society (2,3). Rehabilitation of patients with this type of defect is provided with maxillofacial prostheses, and these patients are reintegrated into society (4). For these reasons; The prosthesis made should be adequate in terms of aesthetics and function, should not have negative effects on the health of the remaining tissues, and should be able to maintain these properties for a long time (5). Even though plastic reconstructive and aesthetic surgery has made great progress today, maxillofacial prostheses are needed in the vast majority of cancer and trauma patients (6). One of the most important advantages of prosthetic rehabilitation in the maxillofacial region compared to surgical operations is that it better adapts to complex anatomical regions (7).

Silicones are the most frequently used materials in the manufacture of maxillofacial prostheses, due to their natural appearance, acceptable physical properties and good color stability (8,9). The duration of use of silicone elastomers used in maxillofacial prosthesis applications is limited to 1-2 years due to the decrease in their physical properties, tears in the margins and changes in their color (3,10). Despite their advantages such as easy manipulation, biocompatibility, and chemical inertness, silicone

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elastomers do not have the desired physical and mechanical properties (8,11). Research continues for a new polymer material with superior mechanical properties such as high tear and rupture strength and low hardness (3).

Tear strength, tensile strength, elongation percentage and hardness tests are used to determine the mechanical properties of silicone elastomers (8). Veres et al. (12) stated that the mechanical properties of an ideal maxillofacial prosthesis material as high tearing, tensile strength, elongation percentage, and low hardness values. Hardness gives information about the softness of materials. The hardness of materials is important for the prosthesis to have a more natural appearance and to adapt to the movements of the head and neck region (8,13). Veres et al. (12) reported that the ideal hardness value should be between 10-40 Shore A.

In terms of ease of use, the first feature desired in a maxillofacial prosthesis is its high tear strength. Tears are occurring quite commonly at the thin edges of the epitheses. The tensile strength of silicone elastomer gives information about the overall strength of the material and is considered an indicator of its elongation flexibility. Elongation percentage is an important parameter in terms of the flexibility of the prosthesis in head and neck movements. High tensile strength and high elongation percentage are the necessary features to prevent deformed prostheses while removed from the tissues (14).

Deteriorations in maxillofacial prostheses usually start from the marginal areas that need to be made thin. The thinly made denture edges are deformed by the effects of cleaners, medical adhesives and body fluids. The most important disadvantages of maxillofacial prostheses are edge tears and ruptures. To eliminate these problems, mechanical properties by adding various fillers such as glass and natural fibers, ceramic fibers, silica powder into silicone elastomers; especially tensile and tear strength is tried to be increased (15,16).

In the chemical industry, research has been undertaken for the past decade to initiate a different industrial process that combines nanoparticles into a polymeric matrix and provides a new class of polymeric materials by presenting the powerful properties of nano oxides. The nano oxide particles are tough and have a higher shear modulus than pure silicone elastomer. The enhanced properties discovered in adding nanoparticles to a polymeric matrix can be attributed to the particle's higher surface energy and chemical reactivity, thereby interacting with the silicone elastomer matrix and forming a 3-dimensional network in the silicon polyethylene structure. Thus, they can improve the physical and optical properties of the organic polymer, as well as provide resistance to environmental stress-induced cracking and aging. These new nano-oxides have been shown to be additive to coatings, rubbers, plastics, sealants, fibers, textiles, and cosmetics. Little has been reported on how the attachment of these particles to a maxillofacial elastomer might affect its properties (17). Nano TiO_2 (titanium dioxide) as an inorganic additive; It has been reported to be biocompatible, chemically stable, and antibacterial (18). The properties of SiO_2 (silica) nanoparticles can be counted as small dimensional structures, large interface areas, active functioning and superior interfacial connection with organic polymer. Thus, protect the structure against cracking and aging by improving the mechanical, optical and physical properties of the organic polymer (17). ZnO (zinc oxide) nanoparticles absorb of A-ultraviolet light and they have antibacterial activity (19).

The mechanical properties that these three nanoparticles with superior properties can impart to elastomers used in maxillofacial prostheses have not been compared in the literature before. This study aims to investigate the mechanical effects of 3 different nano oxide particles (TiO_2-SiO_2-ZnO) by adding them to a commercial silicone elastomer commonly used in an extraoral maxillofacial prosthesis. The null hypothesis of the study is; h0: TiO_2, SiO_2, ZnO nanoparticles addition will not make a difference in the mechanical properties of the silicon elastomer.

MATERIAL AND METHOD

The study was carried out with the permission of Fırat University Non-Interventional Research Ethics Committee (Date: 23.01.2020, Decision No: 02/14).All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, heat polymerized M511 Platinum (Technovent Ltd., England) brand HTV type silicone elastomer which consists of two components, Part A base, and Part B catalyst is used. The weight of the base part of the silicone elastomer in the amount to be sampled was detected using a precision scale (Denver Instrument GmbH, Göttingen, Germany). 2% of the measured weight was calculated and the amount of nanoparticles to be used in the sample was added to the base of the silicon. According to the manufacturer's recommendation, 1/10 of the weight of the base part without nanoparticles was added and the mixing process was started. The mixing process was done with the help of a vacuum mixer (Bego Easy Mix, BEGO, USA) and the silicone elastomer was made ready for polymerization. The mixture prepared for polymerization was placed in molds. In order to determine the number of samples in the study groups, power analysis (power analysis) was applied with the help of the G*Power 3 (Faul, Erdfelder, Lang, & Buchner, 2007) program and the sample number was determined as 11.

To standardize the samples for mechanical tests, metal molds were produced in accordance with the American Society for Testing and Materials (ASTM) standards. For the tensile strength and percent elongation test samples, metal molds were produced based on ASTM D412 (112) standards. The molds to be prepared for the tear strength test samples were made based on ASTM D624 (113) standards (**Figure 1**). Polymerization was carried out in accordance with the manufacturer's recommendation by keeping it at 100 ˚C for 1 hour.

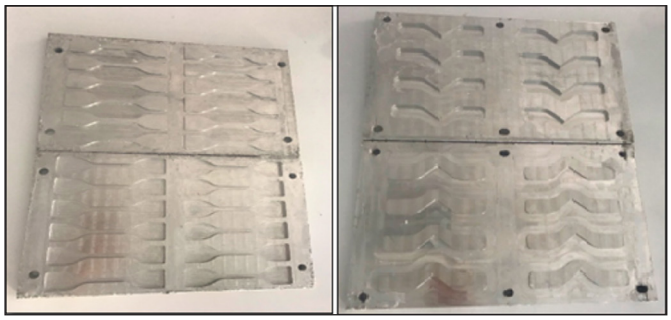

Figure 1. Metal molds prepared for tensile and tear strength tests

Test groups; it consists of 12 groups, with 11 samples (n=11) in each group for the control group and the groups to which nanoparticles were added (TiO_2, SiO_2, ZnO). A total of 132 specimens were produced, 44 for the tensile strength and elongation percentage test, 44 for the tear strength test and 44 for hardness test. For the tensile strength and elongation percentage test, barbell-shaped specimens produced by ASTM D 412 standards were placed in the tensile test device (Llyod Instruments LR 50K, Lyod instruments Ltd, Fareham, England). After the speed of the test device was set to 500 mm/min, the samples were tested. The tensile test was continued until the specimens ruptured. The results were calculated and recorded using the equation; Tensile stress: Load (N)\ Field (mm^2). The percentage of elongation that occurred in the specimen; relative to the first dimension after the rupture occurred in the specimens was calculated using the equation Elongation Percentage (%) = Elongation Amount / First dimension x 100 (**Figure 2**). For the tear strength test, the samples were placed in the same test device. Then the speed of the device was set to 500 mm/min and force was applied at a stable speed. The test was continued until the tearing process was completed. The obtained data were collected using the software of the system. The results were calculated with the formula tear strength = Load (N) / Thickness (mm) (**Figure 3**). For the hardness test, the samples were produced as circular specimens with a diameter of 30 mm and a thickness of 10 mm by ASTM D2240-68 test standards. The samples were prepared by the traditional flask method. Shore A surface hardness test was applied to measure the hardness values of the prepared samples. Five different measurements were made with a digital Shore A test device (Shore Scale Durometer Hardness Tester, England) by determining 5 different points equidistant from the center in each sample. The arithmetic average of the measurements was calculated and recorded as Shore A hardness degree for each sample (**Figure 4**).

Figure 2. Tensile strength and elongation percentage test

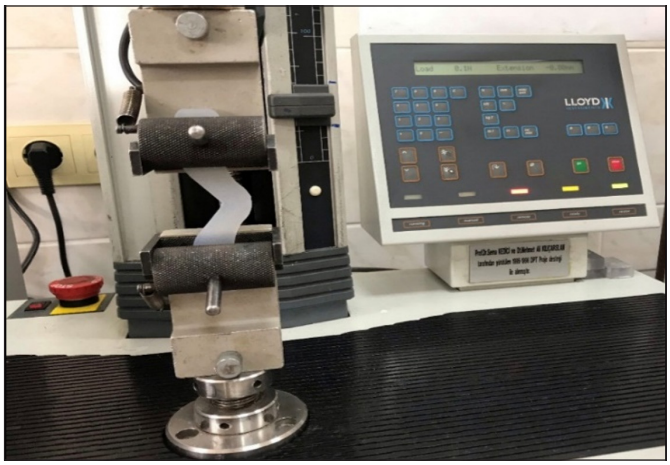

Figure 3. Tear strength test

Figure 4. Hardness measurement with shore a tester

The data obtained for tensile strength, elongation percentage and tear strength test analyzes were analyzed with the IBM SPSS 21 package program. Shapiro Wilk's and/or Kolmogorov Smirnov tests were used due to the number of units while investigating the normal distribution of the variables. When examining the differences between the groups, in case the variables did not come from a normal distribution, the Mann Whitney U test was used for comparisons with two groups, and the Kruskal Wallis-H test for more than two groups. In case of significant differences in the Kruskal Wallis-H test, the groups with differences were determined with the Post-Hoc multiple comparison test. In the evaluation of the groups in terms of hardness, the significant differences between the groups were examined with the Oneway ANOVA Test, and the Tukey HSD Post-Hoc multiple comparison tests were used to determine which groups the significance originated from. While interpreting the results, 0.05 was used as the level of significance; It was stated that there was a significant difference in the case of $p<0.05$, and there was no significant difference in the case of $p>0.05$.

RESULTS

In terms of tensile strength; there was no statistically significant difference between the control-ZnO ($p=0.533$) and TiO_2-SiO_2 ($p=0.309$) groups ($p>0.05$). There was a statistically significant difference between all groups other than these ($p<0.05$). The highest tensile strength mean was found in the SiO_2 added group (3.35 ± 0.18 MPa), and the lowest mean value was found in the control group (2.64 ± 0.27 MPa) (**Table 1**), (**Figure 5**).

In terms of elongation percentage; There was no statistically significant difference between control-ZnO ($p=0.577$), control-SiO_2 ($p=0.577$) and ZnO-SiO_2 ($p=0.67$) groups ($p>0.05$). There was a statistically significant difference between all groups other than these ($p<0.05$). The highest elongation percentage mean value was found in the TiO_2 group (1017.23 ± 89.37 %), while the lowest percent elongation mean value was found in the group with SiO_2 added (900.03 ± 88.92 %) (**Table 2**), (**Figure 6**).

There was no statistically significant difference between only ZnO-TiO_2 groups ($p=0.862$) in terms of tear strength ($p>0.05$). There was a statistically significant difference between all groups other than this ($p<0.05$). The highest tear strength mean was found in the SiO_2 added group (20,84 kN/m), and the lowest mean value was found in the control group (15,51 kN/m) (**Table 3**), (**Figure 7**).

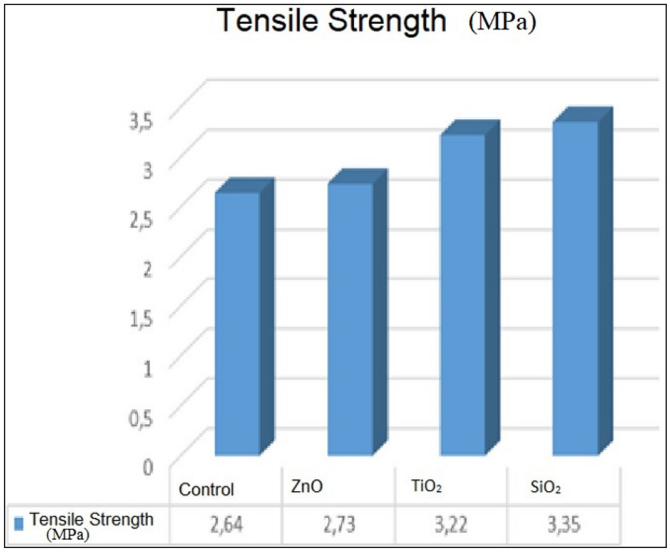

Figure 5. Differences between groups in terms of tensile strength

Table 1. Analysis results regarding the difference between groups in terms of tensile strength

Groups	n	Mean (MPa)	MD (MPa)	Min (MPa)	Max (MPa)	SD	Kruskal Wallis H Test		
							Mean rank	H	p
Tensile strength								24,97	0.001
Control (a)	11	2,64	2,57	2,33	3,25	0,27	11,73		
ZnO (b)	11	2,73	2,86	2,26	3,26	0,32	14,27		
TiO_2 (c)	11	3,22	3,25	2,78	3,71	0,32	29,73		
SiO_2 (d)	11	3,35	3,41	3	3,61	0,18	34,27		
Total	44	2,99	2,99	2,26	3,71	0,41			

* The groups are classified with the letters below, and groups with statistically significant differences are indicated.(p=0.001)a-c, (p=0.001)a-d, (p=0.004)b-c, (p=0.001)b-d.

Table 2. Analysis result regarding the difference between groups in percentage of elongation

Groups	n	Mean	MD	Min	Max	SD	Kruskal Wallis H Test		
							Mean rank	H	p
Elongation percentage								11,25	0,01
Kontrol (a)	11	909,26	898,43	814,25	1145,05	89,37	16,55		
ZnO (b)	11	918,41	948,53	811,96	1058,27	80,95	20,64		
TiO_2 (c)	11	1017,23	972,47	925,24	1151,7	77,61	33,45		
SiO_2 (d)	11	900,03	944,15	715,44	993,27	88,92	19,36		
Total	44	936,23	940,49	715,44	1151,7	94,35			

** The groups are classified with the letters below, and groups with statistically significant differences are indicated. (p=0.002)a-c, (p=0.02)b-c, (p=0.014)c-d.

Table 3. Analysis result regarding the difference between groups in terms of tear strength

Groups	n	Mean (N/mm)	MD (N/mm)	Min N/mm	Max N/mm	SD	Kruskal Wallis H Test		
							Mean rank	H	p
Tear Strength								25,161	0,001
Kontrol (a)	11	15,51	15,64	12,37	17,88	1,79	11,15		
ZnO (b)	11	17,93	18,08	14,2	20,82	1,9	25,5		
TiO_2 (c)	11	17,83	18,33	14,78	19,85	1,61	24,67		
SiO_2 (d)	11	20,84	19,75	18,51	24,72	2,17	39,83		
Total	44	17,98	18,29	12,37	24,72	2,65			

*** The groups are classified with the letters below, and groups with statistically significant differences are indicated. (p=0.006)a-b, (p=0.006)a-c, (p=0.001)a-d, (p=0.006)b-d, (p=0.003)c-d.

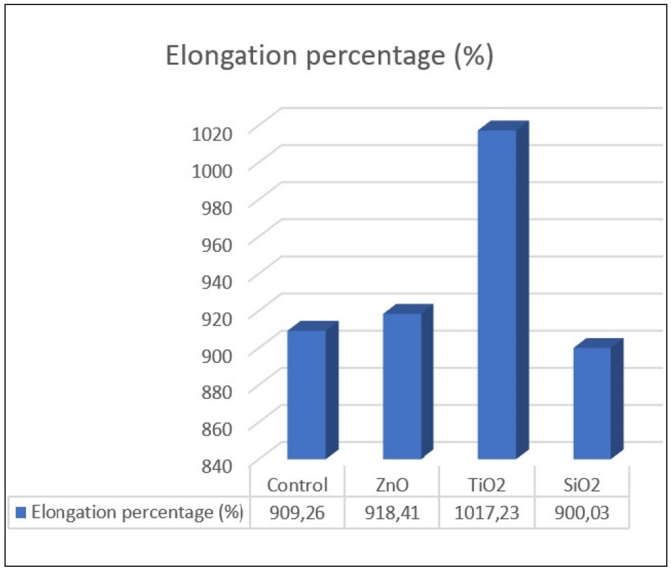

Figure 6. Differences between groups in percentage of elongation

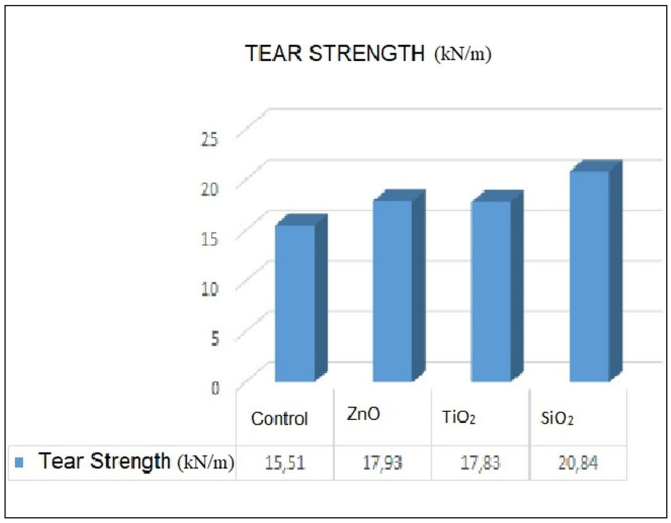

Figure 7. Differences between groups in terms of tear strength

There was no statistically significant difference between only ZnO-TiO_2 (p=0.490) groups in terms of hardness (p>0.05). A statistically significant difference was found between all other groups except this one (p<0.05). The highest hardness mean value was found in the SiO_2 added group (25,50±1,53 Shore), and the lowest mean value was found in the ZnO group (21,85±0,65 Shore) (**Table 4**), (**Figure 8**).

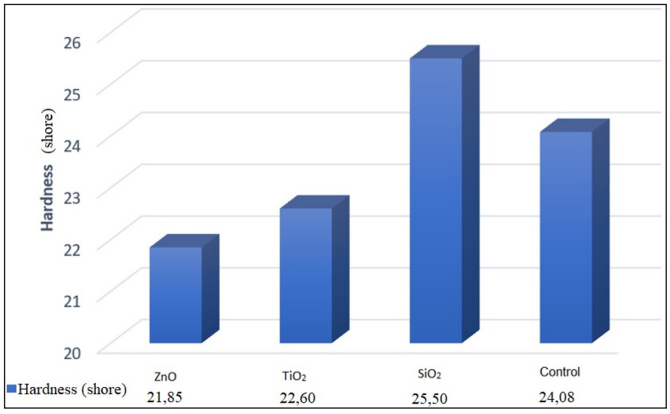

Figure 8. Differences between groups in terms of hardness test

Table 4. Evaluation of groups in terms of hardness

Oneway ANOVA test	Hardness	
	Min-Max	Mean±SD
ZNO (1)	20,5-22,8	21,85±0,65
TiO2 (2)	21,0-23,8	22,60±1,17
SiO2 (3)	23,3-28,3	25,50±1,53
Control (4)	22,8-26,8	24,08±1,17
P		**** 1-3, 2-4, 2-3, 3-4, 1-4,

**** The groups are numbered with the numbers below, and the groups with statistically significant differences are indicated (1-3; p<0.001), (2-4; p=0.001), (2-3; p<0.001), (1-4; p=0.038), (3-4; p=0.047).

DISCUSSION

The null hypothesis of the study was partially rejected. The addition of nanoparticles generally improved the mechanical properties of the silicon elastomer. Lewis and Castleberry (20) reported that not necessary to perform mechanical tests on elastomers under dynamic loads. For this reason, we decided not to apply dynamic loading tests in our study. Craig and Powers (21) stated that the mechanical properties of HTV type silicones are better than RTV type silicones. In our study, HTV type silicone elastomer belonging to the brand M511 was preferred.

Wang et al. (22) added 2%, 4%, and 6% TiO_2 by weight to RTV type MDX4-4210 silicone elastomer, after artificial aging they investigated the effect on its biomechanical properties. As a result of their research, was reported that the addition of 2% TiO_2 by weight improved the mechanical properties of the material, while the addition of 6% TiO_2 reduced the tear strength and elongation

percentage. In this study, the tensile strength (2.80 MPa) of the group to which 2% TiO_2 was added increased in parallel with our study (3.22 MPa) compared to the control group. In the elongation percentage test results, they explained that the test results of the group with 2% added were the highest with the value of 254.28, and that TiO_2 addition decreased the elongation percentage values after a certain. In our study, the addition of TiO_2 increased the elongation percentage values. Values of data are thought to be higher in our study due to the type of silicone elastomer used. Researchers stated that Shore A values increased in direct proportion with the addition of TiO_2. The reason why TiO_2 addition decreased the hardness values in our study; there may be differences in the silicone elastomer used or in the crosslinked structure and density that occurs.

Zayed et al. (23) compared the mechanical properties of RTV type A-2186 silicone elastomer by adding 0.5% - 1% - 1.5% - 2% - 2.5% - 3% by weight SiO_2. Results of the study stated that; there was an increase in tensile strength in all groups, the highest increase was in 3% SiO_2 concentration, the greatest value in the elongation percentage values was observed in the group with 1.5% SiO_2 added, elongation percentage there was a little decrease in the groups with the addition of 2% and 3% SiO_2. There was an increase in the tear strength results in all groups, the highest value was in the group with 3% SiO_2 added. There was an increase in the tear strength results in all groups the highest value was in the group with 3% SiO_2 added, it has been reported that the addition of SiO_2 increases the hardness values. In our study, in parallel with this research, a small decrease in the elongation percentage was detected with the addition of 2% SiO_2.

Nobrega et al. (24) added ZnO, BaSO4, and TiO_2 nanoparticles at 1% and 2% concentrations to silastic MDX4-4210 silicon elastomer and compared their mechanical properties after artificial aging. According to the results of their studies; they reported that hardness, tear strength and permanent deformation values changed in all groups to which nanoparticles were added, that the addition of nanoparticles decreased the hardness values, the highest tear strength occurred in the 1% BaSO4 group, and 1% ZnO group had the lowest permanent deformation value. In our study, while the hardness values increased with the addition of SiO_2, decreased hardness values with the addition of TiO_2 and ZnO show parallelism with this study.

The reasons for obtaining different values in our study from other studies may be factors such as the different physical and chemical properties of the nanoparticles used, cross-linked with silicone elastomer in different configurations and densities, diversity in polymerization methods, storage conditions of test samples, temperature of the room where the mechanical tests are applied, and the sensitivity of the test devices. Not being subjected to artificial aging can be considered a limitation of the study. New methods that can improve the mechanical, biological, optical and physical properties of the materials used in the manufacture of maxillofacial prostheses should be supported by advanced in-vitro and in-vivo research.

CONCLUSION

Within the limitations of this study, the following conclusions could be drawn:

1. The tensile strength of the silicon elastomer was increased with the added nanoparticles. The nanoparticle SiO_2, which provided the greatest increase in tensile strength, was determined as the second TiO_2. Although a slight increase in tensile strength was observed with the addition of ZnO nanoparticles, this result was not statistically significant.
2. The nanoparticle that the most increased the elongation percentage was determined as TiO_2. The increase in percent elongation values of ZnO and SiO_2 particles compared to the control group was not found to be statistically significant.
3. All nanoparticles used increased the tear strength. While the particle that the most increased was SiO_2, no statistically significant difference was found between the groups to which ZnO and TiO_2 were added.
4. It was determined that while SiO_2 nanoparticles increased the hardness value, ZnO and TiO_2 particles decreased it. There was no statistically significant difference between the ZnO and TiO_2 groups.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Fırat University Non-Interventional Research Ethics Committee (Date: 23.01.2020, Decision No: 02/14).

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REFERENCES

1. Fialka-Moser V, Crevenna R, Korpan M, Quittan MJJorm. Cancer Rehabilitation. J Rehabil Med 2003; 35: 153-62.
2. Goiato MC, do Prado Ribeiro P, Pellizzer EP, Idelmo Rangel Garcia J, Pesqueira AA, Haddad MF. Photoelastic analysis of stress distribution in different retention systems for facial prosthesis. J Craniofac Surg 2009; 20: 757-61.
3. Goiato MC, Haddad MF, C Sinhoreti MA, dos Santos DM, Pesqueira AA, Moreno A. Influence of opacifiers on dimensional stability and detail reproduction of maxillofacial silicone elastomer. Biomed Eng Online 2010; 9: 1-9.
4. Hatamleh MM, Watts DC. Mechanical properties and bonding of maxillofacial silicone elastomers. Dent Mater 2010; 26: 185-91.
5. Çevik P. Silika ve titanyum dioksit ilavesinin iki farklı maksillofasiyal silikon elastomerin mekanik özelliklerine etkisi. phD Thesis, Selçuk University Faculty of Dentistry, Department of Prosthodontics, Konya; 2013.
6. Kiat-amnuay S, Gettleman L, Khan Z, Goldsmith LJ. Effect of adhesive retention of maxillofacial prostheses. Part 2: Time and reapplication effects. J Prosthet Dent 2001; 85: 438-41.
7. Wilkes GH, Wolfaardt JF. Osseointegrated alloplastic versus autogenous ear reconstruction: criteria for treatment selection. Plast Reconstr Surg 1994; 93: 967-79.
8. Beumer III J, Curtis TA, Marunick MT. Beumer J, Maxillofacial rehabilitation: prosthodontic and surgical considerations. St Louis: Ishiyaku EuroAmerica, Inc.; 1996:240-285.
9. Yu R, Koran A. Dimensional stability of elastomers for maxillofacial applications. J Dent Res 1979; 58: 1908-9.
10. Han Y, Kiat-amnuay S, Powers JM, Zhao Y. Effect of nano-oxide concentration on the mechanical properties of a maxillofacial silicone elastomer. J Prosthet Dent 2008; 100: 465-73.
11. Mouzakis DE, Papadopoulos TD, Polyzois GL, Griniari PG. Dynamic mechanical properties of a maxillofacial silicone elastomer incorporating a ZnO additive: the effect of artificial aging. J Craniofac Surg 2010; 21: 1867-71.
12. Veres EM, Wolfaardt JF, Becker PJ. An evaluation of the surface characteristics of a facial prosthetic elastomer. Part I: Review of the literature on the surface characteristics of dental materials with maxillofacial prosthetic application. J Prosthet Dent 1990; 63 :193-7.
13. Dootz E, Koran Ar, Craig R. Physical properties of three maxillofacial materials as a function of accelerated aging. J Prosthet Dent 1994; 71: 379-83.
14. Aziz T, Waters M, Jagger R. Analysis of the properties of silicone rubber maxillofacial prosthetic materials. J Dent 2003; 31: 67-74.
15. Andreopoulos A, Evangelatou M, Tarantili P. Properties of maxillofacial silicone elastomers reinforced with silica powder. J Biomater Appl 1998; 13: 66-73.
16. Gunay Y, Kurtoglu C, Atay A, Karayazgan B, Gurbuz CC. Effect of tulle on the mechanical properties of a maxillofacial silicone elastomer. Dent Mater J 2008; 27: 775-9.
17. Han Y, Kiat-amnuay S, Powers JM, Zhao Y. Effect of nano-oxide concentration on the mechanical properties of a maxillofacial silicone elastomer. J Prosthet Dent 2008; 100: 465-73.
18. Garcia-Contreras R, Scougall-Vilchis RJ, Contreras-Bulnes R, Sakagami H, Morales-Luckie RA, Nakajima H. Mechanical, antibacterial and bond strength properties of nano-titanium-enriched glass ionomer cement. J Appl Oral Sci 2015; 23: 321-8.
19. Mouzakis DE, Papadopoulos TD, Polyzois GL, Griniari PG. Dynamic mechanical properties of a maxillofacial silicone elastomer incorporating a ZnO additive: the effect of artificial aging. J Craniofac Surg 2010; 21: 1867-71.
20. Lewis D, Castleberry D. An assessment of recent advances in external maxillofacial materials. J Prosthet Dent 1980; 43: 426-32.
21. Craig R, Powers J. Restorative dental materials. J Biomed Mater Res 2002: 126-53.
22. Wang L, Liu Q, Jing D, Zhou S, Shao L. Biomechanical properties of nano-TiO_2 addition to a medical silicone elastomer: the effect of artificial ageing. J Dent 2014; 42: 475-83.
23. Zayed SM, Alshimy AM, Fahmy AE. Effect of surface treated silicon dioxide nanoparticles on some mechanical properties of maxillofacial silicone elastomer. Int J Biomater 2014; 2014: 750398.
24. Nobrega AS, Andreotti AM, Moreno A, Sinhoreti MA, Dos Santos DM, Goiato MC. Influence of adding nanoparticles on the hardness, tear strength, and permanent deformation of facial silicone subjected to accelerated aging. J Prosthet Dent 2016; 116: 623-9.

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The findings about relationship between autoimmune thyroid disease and first-trimester aneuploidy results

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ABSTRACT

Aim: The aim of this study was to investigate the relationship between thyroid autoantibody and first-trimester aneuploidy results. Thyroid autoimmunity (TAI) is the most common autoimmune disorder. Patients with TAI are usually euthyroid. Thyroid peroxidase (TPO-Ab) in patients with or without thyroid dysfunction is associated with infertility, recurrent embryo implantation failure, and early pregnancy loss. The impact of TPO-Ab on first-trimester aneuploidy test results needs to be studied.

Material and Method: This retrospective case-control study was conducted between December 2019 and May 2022. Patients with thyroid autoantibody positivity (n=112) were included in the study as the case group. The control group was selected from age and body mass index (BMI)-matched patients (n=130). Nuchal translucency (NT), crown rump length (CRL), pregnancy-associated plasma protein A (PAPP-A) and free beta subunit of human chorionic gonadotropin (β-hCG)) values were compared between the two groups.

Results: This study included two hundred forty two age-matched (29.86±4.51) and BMI-matched (23.96±2.34) women. There was no statistically significant difference between groups in terms of free thyroxine (FT4), PAPP-A and free β-hCG (p>0.05). NT as a marker for major chromosomal defects and CRL were comparable in case and control groups (p>0.05).

Conclusion: There is no statistically significant relationship between thyroid autoimmune diseases and the first-trimester aneuploidy results.

Keywords: Aneuploidy, thyroid, autoimmune thyroid disease

INTRODUCTION

Screening for aneuploidy abnormalities has become an important part of prenatal cares and is performed all over the world for pregnant women, especially in the first trimester, and many women want to ensure that their child is healthy before birth (1). The risk of aneuploidy abnormalities increases with increasing maternal age (2). Therefore, screening methods were recommended in the past for women over 35 years old, but these methods are recommended in recent years for all pregnant women (3).

Chromosomal abnormalities can include additional or absent whole chromosomes, and duplications, deletions, and translocations of various sizes. About one out of 150 pregnancies is affected by chromosomal abnormalities which are responsible for 50% of early pregnancy losses (4). Aneuploidy is defined as the existence of one or more additional chromosomes or the lack of one or more chromosomes. The fetal aneuploidy's outcomes differ from incompatibility with life to physical and intellectual disability (5). The prevalence of most common chromosomal aneuploidy is as follows: Down syndrome (with a prevalence of approximately 1 in 700 live births), Edward syndrome (with a prevalence of about 1 in 3,000 live births), Patau syndrome (approximately 1 in 6,000), and Klinefelter syndrome (with a prevalence of 1 in 500 males) (6). The childhood disability considerably affects health system, family, and society (7).

The aim of prenatal screening is to detect the most common types of aneuploidy consistent with survival beyond the early embryologic development into viability (8). Risk can be calculated through evaluation of biomarkers in maternal blood and ultrasound findings with a double test/ combined test in the first trimester and a quadruple/triple test in the second trimester. The combined first-trimester screening between 11+0 to 13+6 weeks of gestation was used as the most effective and standard screening method (9). Crown-rump length (CRL) and Nuchal translucency (NT) assess with the

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ultrasonography for the combined test (9). In addition, the pregnancy-associated plasma protein A (PAPP-A) levels and free beta subunit of human chorionic gonadotropin (β-hCG) check from the maternal blood .(10)

Normal pregnancy and fetal development require thyroid hormone. Placental and fetal development in the first half of pregnancy is dependent on the maternal thyroid hormone supply. Thyroid peroxidase (TPO) as the primary enzyme of the thyroid, is stimulated by thyroid-stimulating hormone (TSH) and it is involved in the production of thyroid hormones. Thyroid Peroxidase Antibodies (TPO-Ab) disrupt the TPO enzymes' normal function causing thyroid inflammation (11).

The autoimmune-related thyroid problems seems to have more common in female population. TPO-Abs are present in 75% of Graves' disease and 90% of cases of Hashimoto's thyroiditis as the most common anti-thyroid autoantibodies (12,13). Thyroid autoimmunity (TAI) is prevalent among women, especially in women with a history of recurrent miscarriage and subfertility (11). TAI describes the existence of circulating anti-thyroid autoantibodies targeted against the thyroid with or without affecting the thyroid function. Thyroglobulin antibodies (TGAb), thyrotropin receptor antibodies (TRAb), and TPO-Ab are the three most clinically important (11).

It is necessary to investigate the prevalence of coexisting of TAI disease and aneuploidy abnormalities. We studied the presence of autoimmune thyroid disease on first-trimester aneuploidy results. The main aim of study investigate the effects of TPOab as TAI disease and fetal health.

MATERIAL AND METHOD

The study was carried out with the permission of Bezmialem University Clinical Researchs Ethics Committee (Date:06.09.2022, Decision No:2022/262). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Two hundred forty two women participated in this study between December 2019 and May 2022.

Women between the ages of 25 and 39 were included in this study and 130 women for the control group, and 112 women with thyroid autoantibody positivity were included in the case group. The exclusion criteria were as follows: 1) known chronic disease other than Hashimoto, 2) over 39 years of age, 3) history of recurrent miscarriage, 4) known chromosomal disorder, 5) history of fetus with anomaly, and 6) medication for thyroid dysfunction.

The inclusion criteria were as follows: 1) 20-39 years old, 2) with known thyroid dysfunction, 3) with three or less pregnancies, and 4) with a body mass index (BMI) between 18.5 and 30.

Anti-TPO, anti-TG, fT3, fT4, TSH were studied with ECLIA (electrochemiluminescence immunoassay) (Roche Diagnostics GmbH, D-68298 Mannheim). TSH was measured with an analytical sensitivity of 0.005 μIU/mL. The anti-TG measurement range is 10–4000 IU/mL, and the anti-TPO measurement range is 5–600 IU/mL. Anti-TG<115 IU/mL, anti-TPO<35 IU/mL were accepted as negative. ELISA (BioVendor, Heidelberg, Germany) was used to measure serum TSH and T4 concentrations.

Ultrasonography of the clear space behind the neck (NT) biochemical tests, including PAPP-A and free β-hCG were performed between 11-13 weeks and six days of pregnancy by operator.

Statistical Analysis

The Kolmogorov-Smirnov test performed to check the normality, and the nonparametric tests performed given the non-normality of the groups before the statistical analyses. Mean and standard deviations (SD) measured to check each continuous variable, including age, BMI, PAPP-A, free β-hCG, TSH, FT4, CRL, Anti-TPO, Anti-TG and NT. The Mann-Whitney U test performed to study the difference between the two groups. SPSS v22 used for statistical analyses. A value of $p < 0.05$ was accepted as statistically significant.

To calculate the sample size with the G-Power 3.1 program, two independent means(two groups) was measured based on the Mann-Whitney test with the allocation ratio N1/N2 =1, the power of 90%, effect size of 40%, and 0.05 type 1 error for at least 216 patients (14).

RESULTS

This study included two hundred forty two age-matched (29.86±4.51) and BMI-matched (23.96±2.34) women. The majority of study participants do not smoke. In the parity of mother, 193 (79.8%) was primipara mother, 49 (20.2%) was nullipara or multipara mothers. **Table 1** shows descriptive statistics of study parameters.

Table 1. Descriptive statistics of study parameters in women

Study parameters	Median (range)	Mean±SD
Maternal characteristics		
Age	29 (20-39)	29.86±4.51
BMI	24 (18.8-29.8)	23.96±2.34
Laboratory values		
PAPP-A(IU/L)	3.115 (0.17-19.3)	3.52±2.55
free β-hCG (IU/L)	36.79 (10.18-779)	46.64±54.76
TSH	2 (1-2.5)	1.8±0.34
FT4	1.2 (0.9-1.8)	1.18±0.14
Anti-TPO	10 (1.1-144)	29.86±28.85
Anti-TG	2.1 (1-126.1)	19.02±23.18
Fetal data		
CRL	55 (45-76)	56.11±6.47
NT	1.5 (1.1-2.5)	1.55±0.32

SD, standard deviation.

Table 2 shows comparison of case and control groups on the study parameters.

Table 2. Comparison of case and control groups

Study parameters	Thyroid autoantibody positive Case (n=112) M±SD	Thyroid autoantibody negative Control (n=130) M±SD	p-value
Laboratory values			
PAPP-A (IU/L)	3.14±1.8	3.85±3.03	0.201
free β-hCG (IU/L)	42.95±26.78	49.82±70.45	0.898
TSH	1.88±0.32	1.74±0.35	<0.001
fT4	1.19±0.1	1.18±0.17	0.208
Anti-TPO	58.26±16.85	5.39±2.54	<0.001
Anti-TG	39.35±19.75	1.5±0.41	<0.001
Fetal data			
CRL	56.12±7.41	56.1±5.55	0.315
NT	1.56±0.33	1.55±0.31	0.850

M, Mean; N, number of subjects; PAPP-A, Pregnancy-associated plasma protein-A; free β-hCG, Free Beta human chorionic gonadotropin; TSH, thyroid-stimulating hormone; FT4, Free thyroxin; CRL, crown-rump length; Anti-TPO, Anti-thyroid peroxidase; Anti-TG anti-thyroglobulin; NT, nuchal translucency scan. All variables tested by a Mann-Whitney U test.

As stated in **Table 2**, a Mann-Whitney test did not find a statistically significant association between case and control in regard to PAPP-A (p>0.05). The control group was relatively higher than the case group (3.85±3.03 vs. 3.14±1.8). There was no statistically significant difference between groups in terms of FT4 and free β-hCG (p>0.05).

There was a statistically significant difference between groups in regard to TSH (p-value<0.001). The case group was statistically higher than control (1.88±0.32 vs. 1.74±0.35).

There was a statistically significant difference between case group and controls in regard to number of Anti-TPO and Anti-TG (p<0.001). The value of Anti-TPO in the case group is ten times more than the control. The value of Anti-TG in the case group is forty times more than the control.

PAPP-A and free β-hCG, along with CRL and NT, are the main parameters of aneuploidy test. There was no statistically significant difference between groups in terms of CRL and NT (p>0.05). CRL and NT values in both groups were nearly similar (56.12±7.41 vs. 56.10±5.55 for CRL) and (1.56±0.33 vs. 1.55±0.31 for NT).

DISCUSSION

In our study, we investigated the impact of thyroid autoantibody positivity on first-trimester aneuploidy results. NT as a marker for major chromosomal defects and CRL were comparable in case and control groups. FT4 was significantly higher in the thyroid autoantibody positive group. PAPP-A and free β-hCG are the major parameters of the aneuploidy test. There was not a statistically significant difference between groups in regard to PAPP-A and free β-hCG.

Based on the conducted studies, the prevalence of TPO-Ab in women is about ten percent. Several studies have been conducted on the effect of TPO-Ab on mother and fetus in recent years. Based on high-quality evidence, TPO-Ab are strongly associated with miscarriage, the development of thyroid disease in pregnancy, and pre-term birth. Weaker evidence suggests that TPO-Ab may also be related to premature rupture of membranes, a higher risk of placental abruption, and maternal anaemia. neurodevelopmental delay, sensorineural hearing loss, and behavioral problems are among the fetal risks associated with TPO-Ab (11).

Identifying the risk factors of aneuploidy abnormalities is very important. The adverse effects of TPO-Ab on the female reproductive system such as infertility, recurrent embryo implantation failure, miscarriages and the fetus's health reported in previous studies were the primary motivation for performing this study.

TPO-Ab was confirmed to be a valuable marker for determining the risk for recurrent miscarriages in many studies (15). Midan et al. (16) reported a significantly higher frequency of antibody-positive among Egyptian women with recurrent miscarriages. Iravani et al. (17) and Lata et al. (18) showed that TAI disease may cause recurrent miscarriages. Somewhat, there are still suspicions about the correlation between recurrent miscarriages and TAI (19,20).

Perminova (21) reported that TAI had adverse effect on endometriosis, idiopathic and endocrine infertility in women. Alexander et al. (22) showed that infertility among women with TAI disease were significantly higher that healthy women. Quintino-Moro et al. (23) reported a significantly higher frequency of TAI disease among infertile women. There are contradictory discussions about the relationship between TAI and assisted reproductive methods. No definitive finding has been reached regarding TAI's adverse effect on in vitro fertilization outcomes (24).

Wasserman et al. (25) reported a significant association between TAI in the third trimester and children's intelligence quotient (IQ). The gap between the IQ of children in the control group at the age of four peaked in comparison with the children of euthyroid mothers. In another study, the same author found the higher risk of hearing deficits in children of euthyroid mothers (26). Another research also reported the relationship between TAI disease and respiratory distress in infants (27), perinatal mortality (28), and intrauterine growth retardation (28). The likely relationship between

maternal TAI disease and fetal neurodevelopmental disorder should be considered vague and awaits further investigations. There are also some studies concerning the effects of day of embryo transfer on aneuploidy tests (29,30).

Although the negative effects of TAI disease on various dimensions of the system are known, the findings of this study did not find the relationship between TAI disease and the first-trimester aneuploidy results. Based on findings, we recommend to do more research parents with abnormalities children in terms of the history of TAI disease. Therefore these results make more accurate findings about the impact of TAI disease on aneuploidy abnormalities.

Based on our findings, we believe several questions remain unanswered in effects of TAI disease on female reproductive system. For this reason, more interventional and observational trials should be done based on more comprehensive multiple-center randomized, and double blinded technique.

CONCLUSION

As a result, there is no statistically significant relationship between TAI diseases and the first-trimester aneuploidy results. TAI leads to infertility and neonatal and pregnancy complications. It is required to conduct more studies to raise our awareness of the possible adverse effects of TAI diseases on the fetus.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bezmialem University Clinical Researchs Ethics Committee (Date:06.09.2022, Decision No:2022/262).

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. Mc Sweeney LC, Monteith C, Kelliher N, et al. 252: Changing patterns of invasive fetal diagnostic testing in the era of NIPT. AJOG 2018; 218: 162-3.
2. Mikwar M, MacFarlane AJ, Marchetti F. Mechanisms of oocyte aneuploidy associated with advanced maternal age. Mutat Res Rev Mutat Res 2020; 785: 108320.
3. Bouariu A, Panaitescu AM, Nicolaides KH. First trimester prediction of adverse pregnancy outcomes-identifying pregnancies at risk from as early as 11-13 weeks. Medicina (Kaunas) 2022; 58: 332.
4. LeFevre NM, Sundermeyer RL. Fetal aneuploidy: screening and diagnostic testing. Am Fam Physician 2020; 101: 481-8.
5. Gregg AR, Gross SJ, Best RG, et al. ACMG statement on noninvasive prenatal screening for fetal aneuploidy. Genet Med 2013; 15: 395-8.
6. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol 2020; 136: 48-69.
7. Shahat ARS, Greco G. The economic costs of childhood disability: a literature review. Int J Environ Res Public Health 2021; 18: 3531.
8. Karadeniz RS, Altay M, Karasu Y, Gelişen O, Haberal A. Comparison of triple and qadrupple test in second trimester Down syndrome screening. GORM 2009; 15: 4-7.
9. Kagan KO, Sonek J, Kozlowski P. Antenatal screening for chromosomal abnormalities. Arch Gynecol Obstet 2022; 305: 825-35.
10. Canick JA, Kellner LH. First trimester screening for aneuploidy: serum biochemical markers. Semin Perinatol 1999; 23: 359-68.
11. Dhillon-Smith RK, Coomarasamy A. TPO antibody positivity and adverse pregnancy outcomes. Best Pract Res Clin Endocrinol Metab 2020; 34: 101433.
12. Saravanan P, Dayan CM. Thyroid autoantibodies. Endocrinol Metab Clin North Am 2001; 30: 315-7.
13. Chardès T, Chapal N, Bresson D, et al. The human anti-thyroid peroxidase autoantibody repertoire in Graves' and Hashimoto's autoimmune thyroid diseases. Immunogenetics 2002; 54: 141-57.
14. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods. 2009; 41: 1149-60.
15. Xie J, Jiang L, Sadhukhan A, et al. Effect of antithyroid antibodies on women with recurrent miscarriage: A meta-analysis. Am J Reprod Immunol 2020; 83: e13238.
16. Midan MF, Elfayoumy KN, El-Bassiony WM, Al-Metwally AA. Thyroid-stimulating hormone in pregnancy: are we in need of a lower cutoff value? BMFJ 2018; 35: 241.
17. Iravani AT, Saeedi MM, Pakravesh J, Hamidi S, Abbasi M. Thyroid autoimmunity and recurrent spontaneous abortion in Iran: a case-control study. Endocr Pract 2008; 14: 458-64.
18. Lata K, Dutta P, Sridhar S, et al. Thyroid autoimmunity and obstetric outcomes in women with recurrent miscarriage: a case–control study. Endocr Connect 2013; 2: 118-24.
19. Wang JW, Liao XX, Li T. Thyroid autoimmunity in adverse fertility and pregnancy outcomes: timing of assisted reproductive technology in AITD women. J Transl Int Med 2021; 9: 76-83.
20. Gungor K, Dokuzeylul Gungor N. Antithyroid antibodies may predict serum beta HCG levels and biochemical pregnancy losses in euthyroid women with IVF single embryo transfer. Gynecol Endocrinol 2021; 37: 702-5.
21. Perminova S. Pathology of the thyroid gland in women with infertility. Klinicheskaya i eksperimental'naya tireoidologiya. 2011; 7: 44-50.
22. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017; 27: 315-89.

23. Quintino-Moro A, Zantut-Wittmann DE, Tambascia M, Machado Hda C, Fernandes A. High prevalence of infertility among women with Graves' disease and Hashimoto's thyroiditis. Int J Endocrinol 2014; 2014: 982705.
24. Venables A, Wong W, Way M, Homer HA. Thyroid autoimmunity and IVF/ICSI outcomes in euthyroid women: a systematic review and meta-analysis. Reprod Biol Endocrinol 2020; 18: 120.
25. Wasserman EE, Pillion JP, Duggan A, et al. Childhood IQ, hearing loss, and maternal thyroid autoimmunity in the Baltimore Collaborative Perinatal Project. Pediatr Res 2012; 72: 525-30.
26. Wasserman EE, Nelson K, Rose NR, et al. Maternal thyroid autoantibodies during the third trimester and hearing deficits in children: an epidemiologic assessment. Am J Epidemiol 2008; 167: 701-10.
27. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. J Clin Endocrinol Metab 2011; 96: 920-4.
28. Männistö T, Vääräsmäki M, Pouta A, et al. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. J Clin Endocrinol Metab 2009; 94: 772-9.
29. Dokuzeylül Güngör N, Gürbüz T, Erşahin AA. The effects of transfer day in intracytoplasmic sperm injection (ICSI) pregnancies on first trimester screening test results. Adıyaman Üni. Sağlık Bilimleri Derg 2018; 4: 1083-93.
30. Dokuzeylül Güngör N, Gürbüz T, Gökmen Karasu AF, Ersahin AA. The alteration of first trimester screening markers in fresh and frozen-thawed blastocyst transfers. EuRj 2019; 5: 686-90.

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Comparison of nutritional status, anthropometric measurements and eating awareness of menopausal women

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ABSTRACT

Aim: The aim of this study is to determine the nutritional status, anthropometric measurements and eating awareness of menopausal women.

Material and Method: The study was conducted with 200 female individuals between the ages of 45-65 who had entered the menopause, living in the Nicosia Gönyeli region of the TRNC and voluntarily accepted to participate in the study. The questionnaire method was applied by interviewing the individuals included in the study face to face.

Results: It was determined that there were statistically significant and negative correlations between the pre-menopausal body weight, current body weight, BMI, waist circumference and hip circumference values, and the Eating Awareness Scale scores ($p < 0.05$). Accordingly, it was found that pre-menopausal body weight, current body weight, BMI, waist circumference and hip circumference values decreased as the Eating Awareness Scale scores increased ($p < 0.05$).

Conclusion: The increase of individuals awareness of eating affects anthropometric measurement values positively. It will help control body weight by gaining eating awareness.

Keywords: Nutritional status, anthropometric measurement, eating awareness, menopausal women

INTRODUCTION

Menopause is a natural process that cannot be avoided for women. Due to the onset of menopause and insufficient estrogen hormone, some metabolic changes occur in the body. Depending on the metabolic changes, the appetite increases, the resting metabolic rate decreases, and the inadequacy of the physical activity level leads to obesity (1). Depending on the hormonal changes of women in the menopause period, weight gain may occur due to the increase in adipose tissue in this period, and obesity, vascular disease and metabolic disorders may develop due to the widespread adiposity in the abdomen, which adversely affects women's health (2). It is a known fact that diet and lifestyle are effective in order to protect health and maintain a quality life with nutrition during and after menopause (3). Being aware of the change in diet; it provides convenience in perceiving the reasons and consequences of the decision made while making food choices and eating habits (4). Wrong choices in food consumption and habits negatively affect the quality of life. Nutrient ratio and balance, excessive fat and carbohydrate intake, irregular meal consumption, insufficient fiber intake, wrong eating behaviors are risk factors for obesity (5). Although awareness is associated with problems that negatively affect many health, it is important to reduce food consumption in healthy food selection and weight loss by providing portion control (6).

This study was planned and carried out to determine the nutritional status, anthropometric measurements and eating awareness of 45-65 years old menopausal women living in the Nicosia-Gönyeli region of the TRNC.

Menopause Risk Factors

Due to the onset of menopause and insufficient estrogen hormone, some metabolic changes occur in the body. Night sweats, hot flashes, irregular sleep, visceral fat and abdominal obesity, which are seen due to these changes, negatively affect the quality of life of women in this period (7). There is an increase in body weight due to hormonal changes and a decrease in metabolic rate and energy expenditure. While this situation improves insulin resistance, it causes an increase in vascular diseases and hyperlipidemia (8). In TURDEP-II study data (9) ; It was observed that the prevalence of obesity increased with increasing age, and the obesity rate was found to be higher in individuals in the 55-59 age group.

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Physical Activity

Exercise programs have an important place for postmenopausal women's life. While regular physical activity reduces the symptoms of menopause, it has been observed that its effects on healthy aging are positive. It is stated that regular application of physical activity during menopause has effects on body weight control, body composition, muscle tissue and bone strength, endurance, blood pressure and metabolism. Postmenopausal women who are physically active have a lower risk of bone fractures (10). Physical activity can significantly reduce the development of chronic diseases such as diabetes, heart problems, blood lipid disorders, high blood pressure and breast cancer (11). It has been found that physical activity is important in minimizing bone loss due to advancing age, regular walking and playing tennis increase muscle strength, and being physically active in every period of life (12).

Nutrition

While consuming daily food and food groups, increasing the diversity and taking the nutrients to the body at a sufficient and balanced level improves the nutritional pattern. It is known that chronic diseases such as obesity, diabetes and even cancer can be prevented with food diversity and it is important for women's health (2). Osteoporosis is an important health problem in women during menopause with advancing age. Excessive protein intake poses a risk for osteoporosis (1). Consumption of animal proteins such as chicken, fish and eggs as needed, but consumption of red meat more than 4 days a week poses a risk (13). Adequate intake of protein, calcium and vitamin D to the body is very important in ensuring proper bone development and preventing age-related bone loss (14). The leading causes of bone loss for the post-menopausal period are estrogen deficiency, increased urinary calcium excretion, decreased calcium absorption from the intestines, and insufficient calcium intake with food (14). Women aged 50 and over are recommended to take 1200 mg of calcium per day (1).

Eating Awareness

Awareness provides convenience in perceiving the reasons and consequences of the decision made while making food choices and eating habits. Skipping meals, eating irregularly, consumption of foods with high energy value but non-nutritive value that adversely affect health cause various diseases such as obesity, increase in plasma blood fat levels, insulin resistance and high blood pressure. Eating awareness supports healthy living and protecting heart health by paying attention to the right timing and appropriate amount for the individual (15). With eating awareness, it can provide healthy weight loss by gaining portion control, meal planning and record keeping skills (16). Upon evaluating arithmetic mean is used and 3 or more score means that the awareness of eating exists.

MATERIAL AND METHOD

The study was carried out with the permission of European University of Lefke University Ethics Board (Date: 28.12.2020, Decision No: 57/01/12/2021/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was carried out with female individuals between the ages of 45-65 years who entered the menopause and voluntarily participated in the research, living in the Nicosia-Gönyeli region of the TRNC between December 2020 and January 2021. For the Gönyeli region in Nicosia, the number of female population was determined as 5583. After statistical calculation according to the random sampling model and population records, the number of samples was calculated as 330. However, due to the pandemic reasons, 200 female individuals were reached. All women included in the study signed the Informed Consent Form. The method of this study is a quantitative research. Questionnaire form, Eating Awareness Scale, International Physical Activity Questionnaire (Short) form were used as data collection tools.

The questionnaire includes demographic information, general information about menopause, questions about eating habits, frequency of food consumption and anthropometric measurements. The questionnaire form was carried out by interviewing the participants face to face.

Eating Awareness Scale (EAS-30)

The scale was first developed by Baer et al. (21) to determine the quality of attention paid to the eating experience. Eating Awareness Scale (EAS-30), which was conducted by Köse et al. (6) in its Turkish, reliability and validity study, consists of 30 questions and 7 sub-factors. The scale's 5-point Likert scale (1: Never, 2: Rarely, 3: Sometimes, 4: Often, 5: Always) is used. Total average point is calculated by summing up the answers to each question.

Anthropometric Measurements

Pre-menopausal body weight, current body weight, height, waist-hip circumference measurements of the individuals participating in the study were taken by the researcher in the questionnaire. The body weights of the individuals were measured with a foot scale in thin clothes and without shoes. Individuals answered their

pre-menopausal weights as an estimate and were recorded in the questionnaire. The heights were measured with the feet side by side and leaning against the wall with a non-flexible measuring tape. In waist circumference measurement, the circumference passing through the middle between the lowest rib bone and the navel was measured with a tape measure. In the measurement of hip circumference, the circumference passing the highest point was measured by standing next to the individual with a non-stretchable measuring tape (17).

Nutritional Habits and Frequency of Food Consumption

Frequency of food consumption is a frequently used method to determine the relationship between disease risk and nutrition. It can be used in different ways according to the purpose, and the amount of food can be questioned according to the frequency of daily, weekly or monthly consumption. In order to determine the frequency of food consumption, a food consumption frequency registration form containing 13 types of food was filled (17). In order to determine the nutritional status of individuals, their eating habits and food consumption frequencies were questioned by face-to-face interviews. Consumption of main and snack meals, reasons for skipping meals or meals, eating speeds, water, salt, tea and coffee consumption were questioned with 14 questions.

Statistical Analysis

The SPSS 25.0 (Statistical Package for Social Sciences) program was used to evaluate the answers given by the women participating in this study to the questions and the data obtained.

Descriptive statistics such as mean, standard deviation, min-max according to anthropometric measurements, age at menarche, menopause and pregnancy status, Eating Awareness Scale scores of female individuals included in the study are given. The Mann-Whitney U test and the Kruskal-Wallis H test for more than two independent variables were used to compare the Eating Awareness Scale scores according to the socio-demographic characteristics, health status, smoking-alcohol habits, general nutritional habits, and activity levels of the women included in the study. In addition, Spearman's test was used to examine the correlation between women's anthropometric measurements and Eating Awareness Scale scores.

RESULTS

When **Table 1** is examined, the mean premenopausal body weight of women is 65.63±10.61 kg, their current body weight is 71.76±11.35 kg, their height is 161.04±5.37 cm, and their BMI is 27.63 ±4.02 kg/m², mean waist circumference values of 91.22±13.93 cm, mean hip circumference values of 106.33±10.28 cm, and mean waist/hip values of females as 0.85±0.07.

Table 1. Anthropometrical measurements of women

	n	x̄	s	Min	Max
Body weight before menopause (kg)	200	65.63	10.61	45	110
Body weight (kg)	200	71.76	11.35	43	120
Height (cm)	200	161.04	5.37	146	175
Body mass index (kg/m²)	200	27.63	4.02	17.5	42.5
Waist circumference (cm)	200	91.22	13.93	62	138
Hip circumference (cm)	200	106.33	10.28	83	135
Waist/hip ratio	200	0.85	0.07	0.66	1.08

Table 2 shows the results for the comparison of the Eating Awareness Scale scores according to the meal consumption status of the women. When **Table 2** was examined, it was determined that the difference between the Eating Awareness Scale scores was significant according to the daily main meal consumption of the women participating in the study ($p<0.05$). There was no significant difference between the Eating Awareness Scale scores according to women's daily snack consumption and meal skipping ($p>0.05$).

Table 2. Eating awareness scale scores according to the meal consumption status of the women

	n	x̄	s	M	SO	χ2/Z	p
Daily main meal consumption						-1.967	0.049*
2 meals	89	106.00	13.33	107.00	92.43		
3 meals	111	108.94	14.05	111.00	106.97		
Daily snack consumption						2.590	0.459
Never	9	112.67	10.93	115.00	122.78		
One time	21	105.14	14.66	109.00	92.52		
Two times	45	108.98	13.63	110.00	107.14		
Three times	125	107.20	13.88	107.00	97.84		
Meal skipping status						-0.642	0.521
Skipping	115	107.21	13.40	108.00	98.24		
Non-skipping	85	108.20	14.34	110.00	103.55		

*p<0,05 χ2: Kruskal-Wallis H testi Z: Mann-Whitney U testi

Table 3 shows the results for the comparison of the Eating Awareness Scale scores according to the distribution of some eating characteristics of women. When **Table 3** was examined, it was determined that there was no significant difference between the Eating Awareness Scale scores according to the way of eating and adding extra salt to the meals ($p>0.05$). Considering the eating speed of female individuals, it was determined that the difference between the scores they got from the Eating Awareness Scale was at a significant level ($p<0.05$). The scores on the Eating Awareness Scale of the women whose eating speed was slow and moderately fast were found to be significantly higher than those who were fast and very fast.

Table 3. Eating awareness scale scores according to the distribution of some eating characteristics of women

	n	$\bar{x}$	s	M	SO	χ2/Z	p	Difference
Way of food consumption								
Non-salty	12	106.67	12.82	110.00	95.92	7.766	0.051	
Low salty	61	110.89	12.60	112.00	113.79			
Normal	118	105.59	14.33	107.00	92.04			
Too salty	9	113.56	11.10	119.00	127.44			
Are you adding extra salt to meals?								
Yes	33	105.94	14.73	106.00	94.79	-0.621	0.535	
No	167	107.96	13.61	110.00	101.63			
Rate of food consumption								
Slow	29	113.28	9.50	113.00	122.31	35.401	0.000*	1-3
Mild rate	106	110.88	12.92	113.00	115.10			1-4
Fast	60	100.92	13.04	101.00	70.34			2-3
Too fast	5	86.60	13.59	87.00	26.30			2-4

*p<0,05 χ2: Kruskal-Wallis H testi Z: Mann-Whitney U testi

Table 4 shows the Spearman test results, in which the correlations between women's anthropometric measurements and Eating Awareness Scale scores are examined. According to **Table 4**, the difference between women's pre-menopausal weight, current weight, waist circumference, BMI, hip circumference values and Eating Awareness Scale scores was found to be statistically significant, and the correlations were found to be negative and low-strength (p<0.05). Accordingly, as the Eating Awareness Scale scores of women increase, their pre-menopausal weight, BMI, current weight, hip circumference and waist circumference decrease.

Table 4. Correlations between women's anthropometric measurements and Eating Awareness Scale scores

		Eating awareness scale
Body weight before menopause (kg)	r	-0.204
	p	0.004*
Body weight (kg)	r	-0.254
	p	0.000*
Height (m)	r	0.010
	p	0.884
BMI (kg/m²)	r	-0.292
	p	0.000*
Waist circumference (cm)	r	-0.262
	p	0.000*
Hip circumference (cm)	r	-0.293
	p	0.000*
Waist/Hip ratio	r	-0.105
	p	0.140

*p<0,05 r: Spearman testi

DISCUSSION

The average body weight of the women included in our study before and after menopause, respectively; It was determined that they were 65 kg and 71 kg, their height was 161 cm on average, and the average BMI values were 27.6 kg/m² (**Table 1**). Sağnak (22), in his study, calculated the average of pre-menopausal and current body weights, respectively; It was determined that 68 kg and 77 kg. In another study, the average weights before and after menopause, respectively; 62 kg and 71 kg, their height is 159 cm, and their BMI is determined as 28.6 kg / m² (18). In the studies conducted by Sağnak and Fakılı (15,22), an increase was observed in premenopausal and current body weights with increasing age. As a result of our study, a similarity was found with an increase in premenopausal and current body weights.

The average waist circumference of the women in our study was 91 cm, the average hip circumference was 106 cm, and the waist/hip ratio of the individuals was 0.85 on average (**Table 1**). In a study, it was determined that menopausal women had a waist circumference of 87 cm, a hip circumference of 104 cm, and a waist/hip ratio of 0.83 for women (19). According to the results of another study, the average waist area of menopausal women is 87 cm, and the average of hip area measurements is 106 cm; ratio was found to be 0.8 cm (18). Studies have shown that the waist/hip ratio exceeds 0.8, which is a risk factor for obesity and is similar to the results of our study.

It was determined that the daily main meal consumption of the women in our study was significantly different from the Eating Awareness Scale scores (p<0.05). The difference between the consumption of snacks and skipping meals of female individuals with the Eating Awareness Scale scores was not found significant (p>0.05) (**Table 2**). The difference between the eating speed of the women included in the study and the scores they got from the Eating Awareness Scale was found to be significant (p<0.05). Eating speed; The scores on the Eating Awareness Scale of the women who were slow and medium fast were found to be significantly higher than those who were fast and very fast (**Table 3**).

It was determined that there was no significant difference between the Eating Awareness Scale scores according to the food consumption style of the women in our study and the status of adding extra salt to the meals (p>0.05) (**Table 3**).

The difference between the pre-menopausal weight, current weight, waist circumference values, BMI and hip circumference values of the women participating in our study was at a significant level with the Eating Awareness Scale scores, and the correlations were found to be negative (p<0.05). Accordingly, as the Eating Awareness Scale scores of women increase, pre-menopausal and current body weight, waist circumference values, BMI and hip circumference values decrease (**Table 4**). Barışkan and Kumsar (20), in the study conducted with the aim of determining the eating awareness of university students, could not find a relationship between the eating awareness of the body and waist circumference. It differs from our study. The reason is thought to be that university students' body perceptions are higher than menopausal women.

In one study: it shows the participants experienced abnormal eating tendencies. Twentyone percent of the participants sometimes avoided eating when they were hungry, 25% were sometimes terrified about being overweight, 82% refused to eat sometimes, and 3% often had the impulse to vomit after a meal. The correlation analysis showed consumption of fruits and vegetables was positively associated to abnormal eating practices, such as binge eating, consuming large quantities of food deliberately out of the sight of other people, and eating alone. A community survey conducted in Australia showed strict dieting, fasting, and binge eating tripled, while purging quadrupled in women 65 years and older (23). The same abnormal eating practices were also found in women 45 to 64 years old, compared to younger women who had similar eating disorders (23).

In another study; it was found that Adult Eating Behaviour had a significant (p< 0.01) impact on Quality of Life. The study stated that postmenopausal had a higher attitude of self-regulation compared to premenopausal women (P = 0.05), Among body composition, eating behaviours and quality of life no between-group differences were observed at the baseline.It was noticed that only food responsiveness had significance difference (24)

CONCLUSION

According to the results of the research, a significant relationship was found between the scores that women got from the eating awareness scale and their BMI values, waist-hip measurements, and body weights. It was found that as the scores obtained from the eating awareness scale increased, these values decreased. In the literature, studies on eating awareness of menopausal women have not been found. It is recommended that similar studies be carried out in the same or different societies, considering that they will contribute to the field. Efforts are necessary for creating nutritional and health awareness among rural women to ensure a better quality of life at menopause.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of European University of Lefke University Ethics Board (Date: 28.12.2020, Decision No: 57/01/12/2021/01).

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. Görgel E, Çakıroğlu F. Menopoz döneminde kadın. Ankara Üniversitesi Basımevi, Ankara 2007: 10-12.
2. Bulmuş GT. Evaluation of the Relationship between nutritional status and frax fracture risk analysis in premenopausal and postmenopausal women: master thesis, Gazi University, Institute of Health Sciences, Ankara 2016.
3. Narsule CK, Sridhar P, Nair D, et al. Percutaneous thermal ablation for stage IA non-small lung cancer: long-term follow-up. J Thorac Dis 2017; 9: 4039-45.
4. St-Onge MP, Ard J. Baskin ML, Chiuve SE, Johnson HM, Krisetherton P. Meal timing and frequency implications for cardiovascular disease prevention: a scientific statement from the American heart association. Circulation; 2017; 135: 96-121.
5. Şanlıer N, Konaklıoğlu E, Güçer E. The relationship between young people's nutritional knowledge, habits and behaviors and body mass indexes. J of Sci Gazi Uni 2009; 25: 333-52.
6. Köse G. A Study on Eating Awareness of University Students. PhD Thesis, Başkent University, Institute of Health Sciences, Ankara 2017.
7. Atasoy M. Hormone: Before and After Menopause. Support Publications, Istanbul 2019.
8. Rakıcıoğlu N. Nutrition in Menopause Period. Ministry of Health, General Directorate of Basic Health Services, Department of Food Safety, Community Nutrition Branch, Ankara 2008.
9. Satman İ, Beyhan Ö, Tütüncü Y, et al. Turkey Diabetes, Hypertension, Obesity and Endocrinologic Diseases Prevalence Study (TURDEP-II) Results 2011.
10. Javadivala Z, Kousha A, Allahverdipour H, AsghariJafarabadi M, Tallebian H. Modeling the relationship between physical activity and quality of life in menopausal-aged women: a cross-sectional study. J Res Health Sci 2013; 17: 168-75.

11. Ağıl A. The effects of different short-term exercise approaches on menopausal symptoms, psychological health and quality of life in postmenopausal women. Master thesis, Başkent University, Institute of Health Sciences, Physical Therapy and Rehabilitation Program, Ankara 2010.
12. Demirgöz M. Sahin NH. Hormonal and non-hormonal pharmacological treatment approaches in perimenopausal hot flashes. Selcuk University, J of Fac Med 2009; 25: 98–106.
13. Paknahad Z, Mohammadifard N, Bonakdar Z, Hasanzadeh A. Nutritional status and its reletionship whith bone mass density in postmenopausal womwn admitted in osteodensitometry center. School of Healty, Isfahan Universty of Medical Sciences, Isfahan-Iran 2015.
14. Demirtaş EM. Investigation of the relationship between food consumption, body composition and some biochemical parameters in postmenopausal women. Master thesis, Hacettepe University, Institute of Health Sciences, Community Nutrition, Ankara 2018.
15. St-Onge MP, Ard J, Baskin ML, Chiuve SE, Johnson HM and Krisetherton P. Meal timing and frequency implications for cardiovascular disease prevention: a scientific statement from the American heart association. Circulation 2017: 96-121.
16. Wansink B. Environmental factors that increase the food intake and consumption volume of unknowing consumers. Annu Rev Nutr 2004: 455-79.
17. Pekcan G. Determination of Nutritional Status, Hacettepe University Faculty of Health Sciences, Department of Nutrition and Dietetics, Ankara 2008.
18. Fakılı FE. Determination of nutritional status and physical activity and nutritional knowledge levels of menopausal individuals. Master Thesis, Başkent University, Institute of Health Sciences, Department of Nutrition and Dietetics, Ankara 2013.
19. Lemay A, Dodin S, Kadri N, Jacques H and Forest J.G. Flaxseed dietary supplement versus hormone replacement therapy in hypercholesterolemic menopausal women. Obstet Gynecol 2002: 495-504.
20. Barışkan H, Kumsar A. Abdominal obesity prevalence and eating awareness levels in health sciences students. J Nurs Educ 2020; 17: 162-9.
21. Baer H. Redoing feminism: Digital activism, body politics, and neoliberalism. Feminist Media Studies 2016: 17-34.
22. Sağnak B. Determination of general nutritional status of menopausal individuals applying to a private clinic in Malatya. Master thesis, Haliç University, Institute of Health Sciences, Department of Nutrition and Dietetics, Istanbul 2015.
23. Hay PJ, M. J., Buttner P, Darby A. Eating disorder behaviors are increasing: findings from two sequential community surveys in south Australia. PLoS ONE 2008; 3: 1541.
24. Özkan S, Alataş ES, Zencir M. Women's quality of life in the premenopausal and postmenopausal periods. Qual Life Res. 2005; 14: 1795–801.

Original Article

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Evaluation of iliotibial band volume with 3T MRI

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ABSTRACT

Aim: The aim of our study is to evaluate the iliotibial band thickness (ITBT) and volume (ITBV) according to age and gender with 3 T MRI in a healthy Turkish population.

Material and Method: In the current study, 150 patients who had knee MRI were retrospectively evaluated. They were divided into the following groups to examine the effects of age: group 1: 18–30 years old; group 2: 31–40 years old; group 3: 41–50 years old; and group 4: 51–60 years old. ITBV measurements were performed on axial T2-weighted knee MR images.

Results: The mean age was 42.2±29.6 (range 18-60) years. The mean ITBT was 1.76±0.22 mm and the mean ITBV was 20,24±1,44 mm3 in all patients. There was statistically significant difference in mean iliotibial band thickness and volume between genders (p=0.001; p=0.001). There were no statistically significant differences in mean iliotibial band thickness and volume values between the groups in the one-way ANOVA test (p >0.05).

Conclusion: Radiological studies on iliotibial band thickness and band area in healthy individuals are new in the literature. This study is the first radiological study in which the volume of the iliotibial band was measured in healthy individuals and was performed on a 3 tesla MR device. Also, it is the first study that is used artificial intelligence for iliotibial band evaluation and the technic is effective and more rapid according to our experience. ITBV and ITBT are statistically significantly higher in males than females. Most thick ITB was detected between the ages of 31-40. The values of our study, especially ITBT, differ from previous studies and the values are altered in a wide range. Therefore, standardization in the calculation is necessary. This topic is open to future research.

Keywords: Artificial intelligence, friction syndrome, iliotibial band, MRI scans

INTRODUCTION

The iliotibial band (ITB) is a lateral thickening of the fascia latae of the thigh. The ITB occurs proximally at the level of the greater trochanter, as the fascial junction of the tensor fascia latae, the gluteus maximus and gluteus medius muscles. It progresses distally, attaches to the supracondylar tubercle of the femoral condyle and distal to the knee joint, to the Gerdy tubercle on the anterolateral aspect of the proximal tibia (1). When the knee is in full extension and flexed 20° to 30°, the ITB lies anterior to the lateral femoral epicondyle and acts as an active knee extensor. At 20° to 30° flexion, the ITB takes a posterior position relative to the lateral femoral epicondyle and becomes an active knee flexor (2).

Friction syndrome occurs as a result of the compression and scouring of different tendon groups between bone and other tendon groups. It is often associated with overuse (3). Iliotibial band friction syndrome (ITBFS) is one of the rare causes of lateral knee pain. Pain is caused by inflammation of the distal portion of the ITB. This syndrome is seen especially in cyclists and runners due to overuse (4). Although the etiology of ITBFS is still unknown, some anatomical variations (limb length difference, genu varum, lower extremity malalignment) excessive pronation, hip adduction weakness, and myofascial restraint was blamed (5). The most accepted cause of ITBFS is, of ITB friction at the level of the lateral femoral epicondyle, it is the compression of the surrounding fat and connective tissue and accordingly the chronic inflammation of ITB (6).

The diagnosis of ITFBS is usually made by physical examination. Typical complaints of the patients are tenderness 1-2 cm above the lateral knee joint and pain that increases with movement in the lateral knee (7). MRI is used to rule out different possible causes and to make a definitive diagnosis. MRI findings are abnormal signal in the adipose tissue between ITB and lateral epicondyle, increased signal in ITB on T2-weighted images, and thickening of ITB (8).

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In the studies carried out so far, the thickness of the most hypertrophic part of the ITB has been measured. There is still no clear study on the normal values of ITB. The aim of this study is to measure the volume of the part of the ITB distal to the lateral femoral epicondyle and its thickness at the level of the lateral femoral condyle, where it is most compressed, using 3T MRI, and evaluate it according to age and gender in the normal population.

MATERIAL AND METHOD

The study was carried out with the permission of Muğla Sıtkı Koçman University Noninvasive Clinical Resarches Ethics Committee (Date: 06.05.2021, Decision No:178). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study was performed in Radiology department. Individuals with any disease (trauma, previous knee surgery, meniscal tear, cruciate ligament tear, collateral ligament tear, those with neurological disease etc.) were excluded from the study. Patient files and imaging findings formed the basis of the study. Generally, patients with nonspecific knee pain were present. Patients with nonspecific symptoms and without pathology who underwent MRI were included in the study. These patients were not diagnosed with any disease during file scans. In the current study, 150 patients who had knee MRIs were retrospectively evaluated. Patients who had knee MRIs in the first 6 months of 2021 were included in the study. Those with poor image quality were excluded from the study.

75 males and 75 females were included in the study. They were divided into groups according to their age and gender: group 1: 18–30 years old; group 2: 31–40 years old; group 3: 41–50 years old; group 4: 51–60 years old; group 5: > 60 years old; group A consisting of 75 men; group B consisting of 75 women. This study was carried out according to the bases of the Declaration of Helsinki. ITBT and ITBV measurements were performed on axial T2-weighted knee MR images. MR images were obtained with a 3 T scanner (Siemens Skyra, Berlin, Germany). Images were obtained with a protocol of 256 × 320 matrix and a 17-cm field of view, repetition time=4200 ms (TR 4200 ms), echo time=43 ms (TE 43 ms), number of excitations=2 (NEX2) and a 2-mm slice thickness.

Volumetric measurement of ITBV was made using 3D Slicer software (3D Slicer software ver. 10.4.2, http://www.slicer.org). The Slicer volumetric measurement program is a free open-source software package developed by Harvard University and approved for medical research. Region of interest (ROI) was adjusted to not exceed the anatomical contours of the band. After dividing the iliotibial band into sections with appropriate threshold values in the axial image, separate MRI numbers were assigned to each image with the slicer software. After each slice containing the relevant iliotibial band sections was revealed and volume calculation was made. Intra-observer variability was set at less than 5% (**Figure 1, 2**).

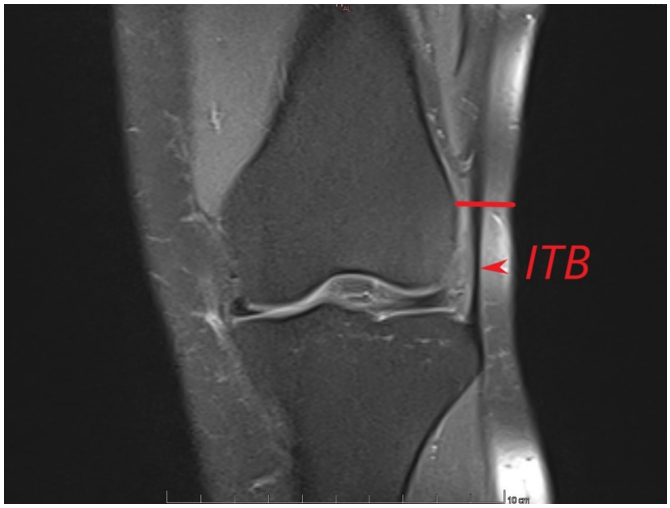

Figure 1. The software calculated ITBV from the proximal point of the tendon, where the lateral condyle makes an angle with the distal metaphysis, to the insertion point.

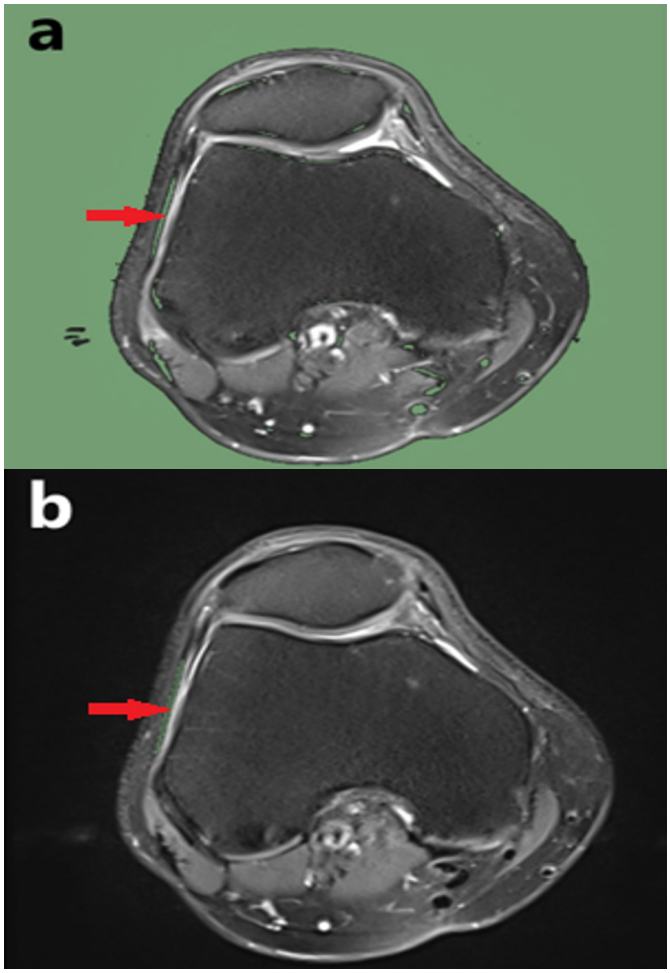

Figure 2. Demonstration of 3D Slicer software a. The software automatically detects tissues in the selected density range, including tendon (marked green). b. Then only the tendon is selected and the tissues outside the tendon are deleted (green part is ITB) so that only ITB can be measured.

Statistical Analysis

Statistical evaluation was performed using IBM SPSS version 20.0 software (IBM Corp, Armonk, NY, USA). The presence of a normal distribution was checked with the Kolmogorov-Smirnov test. Descriptive data are shown as the mean± standard deviation. The independent samples t-test was used to evaluate the significant differences between sexes. One-way ANOVA was used to evaluate the significant differences among age groups. Multiple comparisons were made with the Tukey test. A p value less than 0.05 was accepted as statistically significant.

RESULTS

A total of 150 patients (75 males, 75 females) were included in the study. The interobserver variability was determined at less than 5% for ITBT and ITBV. The mean age was 42,2±29,6 (range 18-60) years. The mean ITBT was 1,76±0,22 mm. The mean ITBV was 20,24±1,44 mm3 in all patients. There was statistically significant difference in mean iliotibial band thickness and volume between sexes (p=0.001; p=0.001). There were no statistically significant differences in mean iliotibial band thickness and volume values between the groups in the one-way ANOVA test (p >0.05).

Table 1. The distribution of age, mean iliotibial band thickness and volume in according to gender

	Males (n=75)	Females (n=75)	P value
Age (years)	39.71±12.7	41.4±11.7	0.371
ITBV (mm3)	21.55±2.08	18.82±1.80	0.001
ITBT (mm)	1.84±0.21	1.70±0.20	0.001

Table 2. The distribution of mean iliotibial band thickness and volume in according to age groups

	18-30 (n=26)	31-40 (n=34)	41-50 (n=44)	51-60 (n=46)
Age (years)	23.33±3.77	36.00±2.47	45.50±2.82	55.07±3.18
ITBV (mm3)	19.99±2.50	20.40±2.49	20.31±2.31	19.58±2.12
ITBT (mm)	1.78±0.23	1.78±0.20	1.77±0.24	1.73±0.21

DISCUSSION

There was statistically significant difference in mean iliotibial band thickness and volume between genders. ITBV and ITBT of males were statistically significant than females. There were no statistically significant differences in mean iliotibial band thickness and volume values between the groups in the one-way ANOVA test (p >0.05). As a measurement, volume and thickness can be alternatives to each other. Instead of manual measurement, automatic measurement parameters can be used as in our study.

There is no statistical difference between age groups. But ITB is thickest between the ages of 31-40. After the age of 40, the numerical values of ITBV and ITBT decrease. ITB's ageing process is similar to other tendons and muscles (9).

Ucpinar et al. (10) found ITB thickness of 2.07+-0.51 in the asymptomatic control group in their study. This study differs from our study in two aspects. First, this is not a volume study. Secondly, the results obtained are different from each other. The reason for this difference is that Ucpinar et al. made measurements while the knee was flexed at 30 degrees. In our study, we performed our measurements while the knee was in full extension in accordance with routine knee MRI protocols. In their study, they also found an average of 2.78± 0.51 ITB thickness in the patient group with friction.

Park et al. (11) average ITBT they measured 1.9±0.4 mm in the normal group and 2.6±0.5 mm in the ITBFS group. They also measured the ITB area in their study and found the mean ITB area was 25.2±6.6 mm2 in the normal group and 38.8±9.1 mm2 in the group with ITBFS. They showed that patients in the ITBFS group had significantly higher ITBCSA and ITBT than those in the normal group. The results of this study are approximately similar to ours. The slight difference between the two studies may be due to the smaller number of patients in their study than ours.

Ekman et al. (12) measured the iliotibial band thickness as 5.49±2.12 mm in the patient group and 2.52±1.56 mm in the control group and showed that the difference was statistically significant. There are differences between the results obtained in our study and the results of this study. Different results between the two studies may be due to two reasons. First, in the study by Ekman et al., the number of patients in the control group was quite low (only 10 patients, 5 females and 5 males). The second is that 8 of these 10 patients have regular athletic activity. Considering the past studies, it is seen that the numerical values are different from each other. This is due to racial differences as well as differences in measurement methods. As far as we know, there is no standard technique for iliotibial band measurement. There is a requirement for standardization in this regard.

ITFBS is one of the important causes of lateral knee pain, which is common in athletes, especially runners. The incidence in athletes is between 1.6% and 12% (13). Although the etiology of ITFBS is still unclear, one of the most accepted theories argues that repetitive friction of the ITB and lateral epicondyle during flexion and extension of the knee joint causes inflammation of the contact area of the ITB. ITB secondary to inflammation becomes edematous and increases in thickness (14). In

our study, we evaluated ITB thickness and volume based on images of patients who did not do any sports, who underwent MRI for nonspecific knee pain and were reported as normal.

Different modalities (US, MRI, stress radiography, computed tomography) can be used in the diagnosis of ITFBS. In cases where ITBFS is considered, MRI is generally used as a diagnostic tool. ITBFS can be diagnosed by the appearance of a high-intensity signal on the T2-weighted image seen at the lateral epicondyle level of the ITB and marked thickening of the distal ITB (15). Ultrasonography can also be used as a diagnostic tool; it shows increased echogenicity in favor of edema at the level of the lateral epicondyle and thickening of ITB. Gyran et al. found a normal ITB thickness of approximately 1.1±0.2 mm in healthy volunteers in their sonographic study (16).

This study has some limitations. Our study is retrospective All the patient's information, physical examination findings and curriculum vitae were obtained through the hospital system. Another there was no equal number of patients in the distribution among age groups.

CONCLUSION

Radiological studies on iliotibial band thickness and band area in healthy individuals are new in the literature. This study is the first radiological study in which the volume of the iliotibial band was measured in healthy individuals and was performed on a 3 tesla MR device. Also, it is the first study that is used artificial intelligence for iliotibial band evaluation and the technic is effective and more rapid according to our experience. ITBV and ITBT are statistically significantly higher in males than females. Most thick ITB was detected between the ages of 31-40. The values of our study, especially ITBT, differ from previous studies and the values are altered in a wide range. Therefore, standardization in the calculation is necessary. This topic is open to future research..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Muğla Sıtkı Koçman University, Noninvasive Clinical Researches Ethics Committee (Date: 06.05.2021, Decision No:178)

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. Flato R, Passanante GJ, Skalski MR, Patel DB, White EA, Matcuk GR Jr. The iliotibial tract: imaging, anatomy, injuries and other pathology. Skeletal Radiol 2017: 605-22.
2. Kaplan EB. Some aspects of functional anatomy of the human knee joint. Clin Orthop 1962; 23: 18-29.
3. Khaund R, Flynn, S. Iliotibial band syndrome: a common source of knee pain. Am Fam Physician 2005; 71: 1545-50.
4. Güney B, Doğan E, Özdemir MY. Osteochondroma as a cause of ischiofemoral impingement- first case series. Acta Med Litu 2021; 28: 189-94.
5. Bankaoglu M, Soydan Mahmutoglu A, Celebi I, et al. Association of iliotibial band friction syndrome with patellar height and facets variations: a magnetic resonance imaging study. Iran J Radiol 2018; 15: e63459.
6. Hong JH, Kim JS. Diagnosis of iliotibial band friction syndrome and ultrasound guided steroid injection. Korean J Pain 2013; 26: 387-91.
7. Yan R, Huang Z, Wang L, Zhang X. MR manifestations and clinical significance of iliotibial band friction syndrome. Zhonghua Yi Xue Za Zhi 2014; 94: 1473-5.
8. Ellis R, Hing W, Reid D. Iliotibial band friction syndrome--a systematic review. Man Ther 2007; 12: 200-8.
9. Seeber GH, Wilhelm MP, Sizer PS Jr, et al. The tensile behaviors of the iliotibial band - a cadaveric investigation. Int J Sports Phys Ther 2020; 15: 451-9.
10. Agridag Ucpinar B, Bankaoglu M, Eren OT, Erturk SM. Measurement of iliotibial band diameter in iliotibial band friction syndrome and comparison with an asymptomatic population. Acta Radiol 2021; 62: 1188-92.
11. Park J, Cho HR, Kang KN, et al. The role of the iliotibial band cross-sectional area as a morphological parameter of the iliotibial band friction syndrome: a retrospective pilot study. Korean J Pain 2021; 34: 229-33.
12. Ekman EF, Pope T, Martin DF, Curl WW. Magnetic resonance imaging of iliotibial band syndrome. Am J Sports Med 1994; 22: 851-4.
13. Strauss EJ, Kim S, Calcei JG, Park D. Iliotibial band syndrome: evaluation and management. J Am Acad Orthop Surg 2011; 19: 728-36.
14. Ferber R, Noehren B, Hamill J, Davis IS. Competitive female runners with a history of iliotibial band syndrome demonstrate atypical hip and knee kinematics. J Orthop Sports Phys Ther 2010; 40: 52-8.
15. Vasilevska V, Szeimies U, Stäbler A. Magnetic resonance imaging signs of iliotibial band friction in patients with isolated medial compartment osteoarthritis of the knee. Skeletal Radiol 2009; 38: 871-5.
16. Gyaran IA, Spiezia F, Hudson Z, Maffulli N. Sonographic measurement of iliotibial band thickness: an observational study in healthy adult volunteers. Knee Surg Sports Traumatol Arthrosc 2011; 19: 458-61.

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Effects of maternal dietary patterns and maternal obesity on children's obesity

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ABSTRACT

Aim: The effects of dietary patterns and dietary statuses of mothers on childhood obesity have not been understood clearly yet. This study aims to evaluate the dietary patterns of mothers and their dietary statuses on the obesity of children.

Material and Method: This cross-sectional study included 295 mothers and their children, who were 2-6 years old. The participants' anthropometric measurements were carried out and the frequency of food consumption was also collected from the mothers in the study.

Results: In the study, it was determined that the children of the participating mothers, who had high levels of income and education, had higher probabilities of being overweight/obese. Overweight/obesity in children was found to be significantly associated with maternal overweight/obesity (B=4.04, p<0.001).The results of our analyses demonstrated that maternal bread, rice, and sugar intake was strongly correlated with children's obesity (B=3.65, p<0.001; B=3.17, p<0.001; B=8.32, p<0.001). In terms of the cards that were shown to the children, it was determined that the children preferred unhealthy snacks, such as biscuits, wafers, and carbonated drinks, more frequently rather than healthy food while preferring watching television and playing games on computers rather than physical activities.

Conclusion: As the variables of income level, education level, BMI values, and consumption of bread, rice, and sugar in mothers were increased, it was determined that the probability of obesity in children, who were 2-6 years old, also increased. These results indicated hopeful outcomes in terms of preventing obesity in children by keeping the dietary patterns of mothers under control.

Keywords: Maternal obesity, childhood obesity, maternal food consumption

INTRODUCTION

The prevalence of childhood obesity has been increasing in every country. The World Health Organization (WHO) stated that approximately 42 million children and adolescents were affected by overweight or obesity in 2013 (1). According to the data of Turkey Nutrition and Health Survey 2010, it was determined that the prevalence of obesity was 8.5% for 0-5 years old children while the prevalence of children with overweight was 17.9% in addition to the total ratio of 26.4% for children with overweight and obesity (2). As a result of an obesity prevalence study, which was conducted by Olaya et al. (2017) in 7 European countries, it was determined that Turkey was ranked the 2nd (3).

Obesity can result in short-term and long-term outcomes. Children with overweight and obesity are at risk of hyperlipidemia, hypertension, insulin resistance, and Type 2 diabetes (4). Furthermore, children with overweight and obesity are candidates for adults with obesity in the future. Childhood obesity also increases the prevalence of chronic diseases in adulthood (5).

Various factors, such as genetic factors, metabolic influences, physical activity, nutrition, environmental elements, socioeconomic factors, and physiological factors, increase the prevalence of obesity (6,7). The skills that are gained during childhood influence children's choices of food, attitudes toward food, and nutritional habits in the future. Attitudes of family members toward food and the interactions within families also play significant roles in children's healthy choices and weight gains (8-10). In numerous studies, the relationships between the anthropometric measurements of children and parents have been

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investigated. In this study, we aimed to investigate the effects of a mother's nutritional patterns and nutritional status on children's obesity, which was considered lacking in the literature.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara University Ethics Committee (Date: 04.09.2014, Decision No:183/12). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Data Collection

The data of the study were collected from 295 mothers, who were between 20 and 45 years old, and their children, who were between 2 and 6 years old. The mothers and children in the study visited the Primary Health Service Center in Ankara. All the families with children in this age group were contacted by phone and were informed about the study. The subjects were asked to volunteer to participate in the study and were asked to direct their children to the Primary Health Service Center. Informed consent was obtained from the mothers.

Anthropometric Measurements

The anthropometric measurements of the study were collected to evaluate the nutritional status of the subjects. The body weights and heights of the children were also recorded. Accordingly, the body mass indices (BMI) were calculated in kg/m². In the measurements, all the children stood barefooted against a vertical wall and their heights were measured by using a stadiometer with the closest interval of 0.1 cm. The body weights of the children were measured while they were wearing lightweight clothes by using a digital scale with a closest interval of 0.1 kg, which was zeroed before the initiation of the weight measurements. Considering the WHO growth reference data (11), 3 weight categories were created, which covered normal (>5th percentile to <85th percentile), overweight (>85th percentile to <95th percentile), and obesity categories (≥ 95th percentile). The weight measurements of the mothers were conducted by using electronic scales with the closest interval of 0.1 kg while their heights were measured with light clothes and without shoes by using a wall-mounted stadiometer with the closest interval of 0.1 cm. The body mass indices were calculated according to the WHO standards. The underweight category covered the BMI values less than 18.5 kg/m² while the normal weight category covered the BMI values between 18.5 and 24.9 kg/m². The BMI values that were between 25.0 and 29.9 kg/m² were categorized as overweight while the BMI values that exceeded 29.9 kg/m² were affected by obesity (12).

Evaluation of Food Consumption Frequency

The data for the diet of the mothers were collected by using a food-frequency questionnaire. In the evaluation of the food consumption frequency, the recommendations in the Dietary Guidelines for Turkey-Specific Nutrition Guide (13). According to the data that were obtained in the study, the food consumption of the subjects was classified into 3 groups as consuming less than the recommended amounts, consuming as much as the recommended amounts, and consuming more than the recommended amounts.

Investigation of Preferences of Children toward Nutrition and Physical Activities

To investigate the preferences of children toward nutrition and physical activities, 10 cards were prepared. Of these, 8 cards presented images of healthy and unhealthy food while 2 cards presented images of physical activities. In the investigation process, the children in the study were shown the cards and asked about their preferences in the food and physical activities in the cards. Then, the responses of the children were recorded.

Statistical Analyses

The statistical analyses in the study were conducted by using SPSS 21 (Statistical Package for Social Sciences) software for Windows. The normality tests for the continuous variables were conducted by the Kolmogorov-Smirnov test. Accordingly, it was determined that all of the continuous variables had normal distributions ($p>0.05$). For the data with normal distributions, the descriptive statistics were presented as mean±standard deviation. On the other hand, the categorical data were presented in figures (percentages). The one-sample t-test was used to evaluate the differences in mean values of the children's anthropometric measurements. Furthermore, a logistic regression analysis was conducted to test the hypothesis that certain demographic variables and the number of daily food consumptions of mothers could affect children's BMI values. The suitability of the data set for logistic regression analysis was tested by using the Hosmer Lemeshow test, where it was determined that the data set was suitable for logistic regression analysis ($p=0.153$). Accordingly, the Nagelkerke R-squared value of the model was determined as 0.893 while the classification success of the model was determined as 95.8%. For all the statistical comparisons, the level of significance was regarded as 5% ($p<0.05$).

RESULTS

The descriptive data of the children in the study were presented in **Table 1**. Accordingly, it was determined that 49.2% of the children were females while 50.8% of the children were males. The mean age of the children was

calculated as 4.2±1.2 years. The difference between the heights and body weights of female and male children was not statistically significant (p>0.05). However, the difference between the BMI values of male and female children was statistically significant and the values were statistically higher in male children (p=0.001).

Table1. Descriptive statistics of the children according to the variable of gender

Variables	Males	Females	p*	Total
N (%)	150 (50.8)	145 (49.2)		295
Age	3.9±1.3	4.2±0.9	0.182	4.2±1.2
Height (cm)	102.1±9.0	104.4±9.3	0.141	103.1±9.2
Weight (kg)	17.3±3.6	17.4±3.5	0.845	17.3±3.5
BMI (kg/m²)	16.8±1.7	16.0±1.4	0.001	16.4±1.6

*One sample t test

The descriptive statistics for the mothers were presented in **Table 2.** Accordingly, it was determined that the mean age of the mothers was 32.7±5.04 years while the mean BMI value of the mothers was 27.3±4.2 kg/m². Additionally, it was determined that 59% of the mothers were affected by overweight or obesity while most of them had moderate-level incomes (49.5%) in addition to 45.4% of the mothers who had undergraduate degrees.

Table 2. Descriptive statistics of the mothers

Age and anthropometric measurement (mean±standard deviation)	
Age (years)	32.7±5.04
Height (cm)	163.2±6.1
Weight (kg)	67.4±10.4
BMI (kg/m²)	27.3±4.2
BMI category, N (%)	
Normal	121 (41.0)
Overweight/obese	174 (59.0)
Income level, N (%)	
Low	90 (30.5)
Moderate	146 (49.5)
High	59 (20.0)
Maternal education, N (%)	
High school and lower	131 (44.4)
Undergraduate	134 (45.4)
Graduate and above	30 (10.2)

A logistic regression analysis was conducted to test the hypothesis that certain demographic variables and daily nutritional amounts of mothers could affect the BMI values of children. The results of this analysis were presented in **Table 3.**

In the study, it was determined the children, whose mothers had income levels above the minimum wage in Ankara, and had education levels of high school and above, had 1.87 and 0.58 times higher probabilities of affecting by overweight/obesity, respectively (p<0.05).

It was further determined that the children, whose mothers were affected by overweight/obesity, had 4.04 times higher probabilities of affecting by overweight/obesity. Additionally, it was discovered that male children had 2.46 times higher probabilities of affecting by overweight/obesity compared to female children (p<0.001).

According to the recommendation of Dietary Guidelines for Turkey-Specific Nutrition Guide, the children, whose mothers had high levels of daily bread, rice, and sugar consumption, 3.65, 3.17, and 8.32 times higher probabilities of affecting by overweight/obesity, respectively.

Table3. Results of logistic regression analysis

Items	Children's BMI levelsa		p
	Normal Weight	Overweight/ obese ExpB (Lower-Upper of 95% CI)	
Demographic variables			
Maternal Income (above the minimum wage compared to those who are not)	1.00 (Ref.)	1.87 (1.04-3.35)	0.036
Maternal Education (having high school degree compared to those who do not)	1.00 (Ref.)	0.58 (0.10-1.11)	<0.001
Maternal Age	1.00 (Ref.)	0.98 (0.93-1.04)	0.576
Maternal BMIb (obese/ overweight compared to those who are not)	1.00 (Ref.)	4.04 (2.41-6.75)	<0.001
Gender of children (males compared to females)	1.00 (Ref.)	2.46 (1.48-4.08)	<0.001
Age of children	1.00 (Ref.)	0.89 (0.72-1.10)	0.290
Daily maternal food intakec (over-consuming compared to those who do not)			
Milk	1.00 (Ref.)	0.71 (0.42-1.20)	0.200
Cheese	1.00 (Ref.)	0.50 (0.23-1.01)	0.083
Meat	1.00 (Ref.)	1.02 (0.58-1.79)	0.944
Legumes	1.00 (Ref.)	1.43 (0.88-2.33)	0.153
Egg	1.00 (Ref.)	1.23 (0.75-2.04)	0.412
Bread	1.00 (Ref.)	3.65 (1.98-6.72)	<0.001
Rice	1.00 (Ref.)	3.17 (1.62-6.22)	<0.001
Vegetables	1.00 (Ref.)	1.19 (0.72-1.65)	0.501
Fruits	1.00 (Ref.)	1.09 (0.63-1.91)	0.752
Sugar	1.00 (Ref.)	8.32 (4.61-15.02)	<0.001
Fat	1.00 (Ref.)	1.19 (0.73-1.94)	0.481

a The dependent variable is categorized as normal and overweight/obese while BMI z-score is calculated by using WHO growth charts (overweight/obese defined as BMI percentile ≥85th-<95th, normal weight defined as BMI percentile ≥15th-<85th).
bMaternal BMI is categorized as normal and overweight/obese (normal as BMI<25 kg/m², overweight/obese as BMI≥25 kg/m²).
cWhile evaluating the frequency of food consumption, the amounts recommended in the Dietary Guidelines for Turkey were taken as the reference.

In the study, it was aimed to determine the preferences of children by presenting them with cards that included healthy and unhealthy preferences. Accordingly, it was determined that the BMI values of the mothers and the preferences of children in diet and physical activity were

similar (p<0.05). In the analysis, it was discovered that most of the children preferred biscuits instead of yogurt, wafers instead of apples, carbonated beverages instead of ayran, cola instead of milk in addition to preferring watching television and playing games on computers instead of riding bicycles and playing basketball (**Table 4**).

Table 4. Relationships between BMI values of the mothers and the preferences of children in diet and physical activity

Cards	Which is healthier?	Maternal BMI levelsa		p
		Normal weight	Overweight/ obese	
1	Boiled potatoes (n, %)	51 (42.1)	91 (52.3)	0.086
	Fried potatoes (n, %)	70 (57.9)	83 (47.7)	
2	Honey (n, %)	75 (62.0)	116 (66.7)	0.408
	Chocolate Spread (n, %)	46 (38.0)	58 (33.3)	
3	Fruits (n, %)	90 (74.4)	122 (70.1)	0.423
	Cake (n, %)	31 (25.6)	52 (29.9)	
4	Biscuit (n, %)	83 (68.6)	114 (65.5)	0.581
	Yoghurt (n, %)	38 (31.4)	60 (34.5)	
5	Nuts (n, %)	72 (59.5)	115 (66.1)	0.248
	Chips (n, %)	49 (40.5)	59 (33.9)	
6	Wafer (n, %)	85 (70.2)	122 (70.1)	0.980
	Apple (n, %)	36 (29.8)	52 (29.9)	
7	Carbonated drink (n, %)	80 (66.1)	120 (69.0)	0.606
	Ayran (n, %)	41 (33.9)	54 (31.0)	
8	Cola (n, %)	99 (81.8)	126 (72.4)	0.062
	Milk (n, %)	22 (18.2)	48 (27.6)	
9	Watching TV (n, %)	82 (67.8)	122 (70.1)	0.668
	Cycling (n, %)	39 (32.2)	52 (29.9)	
10	Playing games on computers (n, %)	74 (61.2)	107 (61.5)	0.953
	Playing basketball (n, %)	47 (38.8)	67 (38.5)	

aMaternal BMI is categorized as normal and overweight/obese (normal as BMI<25 kg/m2, overweight/obese as BMI≥25 kg/m2).

DISCUSSION

Childhood is a critical period for developing obesity. The dietary patterns gained in this period can affect the whole life. The dietary patterns of mothers, dietary status, and food preferences also pose examples for children to gain healthy dietary patterns. The current study is the one of the rare that comprehensively examined the effects of maternal dietary patterns and dietary status on children with obesity.

In this study, although the heights and body weights of male and female children were determined to be similar, the BMI values of male children were higher compared to the BMI values of female children in statistically significant terms (p=0.001). Similarly, in previous studies, it was reported that the BMI values of male children were higher compared to female children (14-16). In a study conducted in Portugal, it was reported that 8.2% of the children in the 3-10 years old group were affected by obesity (15) while a study that was conducted in Germany reported that 4.4% of the children in the 2-7 years old group were affected by obesity (16). In another study in China, it was reported that the prevalence of obesity in a group that contained children and adolescents was 5.6% (17). In the current study, 10% of the children, which is a significant portion, were affected by obesity.

The most important causes of childhood obesity include calorie intake more than the spent calories and lack of physical activity. The factors that cause children to take more calories than necessary include working mothers and high levels of income. When mothers work, they may not spare time for preparing meals. In a study conducted by Gershuny and Fisher (18), it was reported that the mothers who did not work cooked more frequently compared to mothers who worked. Additionally, it was reported that because children were not under the sound care of their mothers, they were more inclined to prefer unhealthy food and did less physical activities (19, 20). Several studies also reported that the access of children became easier as the income levels of mothers were increased in addition to increased frequencies of consuming ready-made meals (18, 21, 22). In the current study, it was determined that the probability of children affecting by obesity was increased as the income and education levels of the mothers were increased.

Similar to numerous previous studies, in the current study, it was determined that the children, whose parents were affected by overweight/obesity, were also affected by overweight and obesity (14-16, 23, 24).

The results indicated that the dietary patterns of parents were especially vital for the dietary patterns of children. Several studies reported that the dietary patterns of parents and children were related to each other (25-27). In a study conducted by Tang et al. (28), it was reported that the mother's consumptions of grains, vegetables, and snacks were positively related to the BMI values of children. In the current study, it was determined that the children, whose mothers consumed high levels of bread, rice, and sugar, had higher probabilities of affecting by overweight/obesity.

Various studies reported that children who were younger than 8 years old preferred sweet drinks, candies, bread, and snacks with high carbohydrate contents instead of healthy food such as vegetables, fruits, and whole grains (29, 30). It was also determined that children preferred spending time watching television and using computers (31,32). In the current study, it was determined that the children preferred unhealthy snacks, such as biscuits, wafers, and carbonated beverages, more frequently compared to healthy foods while preferring watching television and playing computer games instead of doing physical activities.

CONCLUSION

The results of this study demonstrated that maternal body weight and dietary patterns were significantly related to children with overweight/obesity. Especially, maternal consumption of bread, rice, and sugar had positive effects on children with overweight/obesity. Mothers with obesity were a predictor of obesity in children. Maternal dietary habits might play a role in the development of young children's dietary patterns. Mothers should also be encouraged to improve their dietary knowledge, and healthy foods should be made available in an easier way, which can allow mothers to guide their children to develop beneficial dietary patterns and to achieve a fine nutritional status..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara University Ethics Committee (Date: 04.09.2014, Decision No:183/12).

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. World Health Organisation (WHO). Interim Report Of The Commission On Ending Childhood Obesity. Geneva, 2015. https://www.who.int/end-childhood-obesity/commission-ending-childhood-obesity-interim-report.pdf?ua=1. Accessed October 16, 2021.
2. Turkey Nutrition and Health Survey (TBSA). Report on the Assessment of Nutrition Status and Habits. T. R. Ministry of Health, Ankara, 2014. https://hsgm.saglik.gov.tr/depo/birimler/saglikli-beslenme-hareketli-hayat-db/Yayinlar/kitaplar/diger-kitaplar/TBSA-Beslenme-Yayini.pdf. Accessed January 08, 2021.
3. Olaya B, Moneta MV, Pez O, et al. Country-level and individual correlates of overweight and obesity among primary school children: a cross-sectional study in seven European countries. BMC Public Health 2015; 15: 475.
4. Kelly AS, Barlow SE. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches. Circulation 2013; 28: 1689-712.
5. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet 2011; 378: 815–25.
6. Krebs NF, Himes JH, Jacobson D, Nicklas TA, Guilday P, Styne D. Assessment of child and adolescent overweight and obesity. Pediatrics 2007; 120: 193-228.
7. Lobstein T, Baur L, Uauy. Obesity in children and young people: a crisis in public health. Obes Rev 2004; 1: 4-104.
8. Liu Y, Chen HJ, Liang L, Wang Y. Parent-child resemblance in weight status and its correlates in the United States. PLoS One 2013; 8:e65361.
9. Turan T. Okul Öncesi Eğitime Devam Eden Çocukların (3-6 Yaş) Beslenme Alışkanlıklarının, Beden Kitle İndekslerine ve Beslenme Kaynaklı Sağlık Sorunu Yaşamalarına Etkisini İnceleme. Yüksek Lisans Tezi. Maltepe Üniversitesi, İstanbul. 2016. http://openaccess.maltepe.edu.tr/xmlui/handle/20.500.12415/4042. Accessed November 10, 2021.
10. Wang Y, Beydoun M, Li J, Liu Y, Moreno LA. Do children and their parents eat a similar diet? Resemblance in child and parental dietary intake–systematic review and meta-analysis. J Epidemiol Community Health 2011; 65: 177–89.
11. World Health Organization (WHO). AnthroPlus for personal computers manual: software for assessing growth of the world's children and adolescents. Geneva, 2009. https://www.who.int/growthref/tools/who_anthroplus_manual.pdf. Accessed January 23, 2021.
12. World Health Organization (WHO). Physical status: The use and interpretation of anthropometry. Report of the WHO Expert Committee. Technical Report Series. Geneva, 1995. https://apps.who.int/iris/handle/10665/37003. Accessed January 23, 2021.
13. TOBR. Turkey-Specific Nutrition Guide. Hacettepe University Department of Nutrition and Dietetics. Ankara, 2004.
14. Andegiorgish AK, Wang J, Zhang X, Liu X, Zhu H. Prevalence of overweight, obesity, and associated risk factors among school children and adolescents in Tianjin, China. Eur J Pediatr 2012; 171: 697–703.
15. Bingham DD, Varela-Silva MI, Ferrao MM, Augusta G, Mourao MI, Nogueira H, Marques VR, Padez C. Socio-demographic and behavioral risk factors associated with the high prevalence of overweight and obesity in Portuguese children. Am J Hum Biol 2013; 25: 733–42.
16. Hoffmann SW, Tug S, Simon P. Child-caregivers' body weight and habitual physical activity status is associated with overweight in kindergartners. BMC Public Health 2014; 14: 822.
17. Xi B, Mi J, Duan JL, Yan SJ, Cheng H, Hou DQ, Zhao XY. Familial clustering of obesity and the role of lifestyle factors among children in Beijing (in Chinese, English abstract). Zhonghua Yu Fang Yi Xue Za Zhi 2009; 43: 122-7.
18. Gershuny Jonathan, Fisher Kimberly. Leisure. In: Halsey A.H., Webb J., editors. Twentieth-century british social trends. 3rd Edition. Macmillan Publishers Ltd; London, 2000. pp. 620–49.
19. Klesges Robert C, Stein Risa J, Eck Linda H, Isbell Terry R, Klesges Lisa M. Parental influence on food selection in young children and its relationships to childhood obesity. The Am J Clin Nutr 1991;53: 859–64.
20. Cawley J, Liu F. Maternal employment and childhood obesity: a search for mechanisms in time use data. Economics Human Biology 2012; 10: 352–64.
21. Monsivais P, Aggarwal A, Drewnowski A. Time spent on home food preparation and indicators of healthy eating. American Journal of Preventive Medicine 2014; 47: 796–802.
22. Watanabe E, Lee JS, Kawakubo K. Associations of maternal employment and three-generation families with pre-school children's overweight and obesity in Japan. Int J Obes 2011; 35: 945–52.
23. Egmond-Fröhlich AW, Widhalm K, de Zwaan M. Association of symptoms of attention-deficit/hyperactivity disorder with childhood overweight adjusted for confounding parental variables. Int J Obes (Lond) 2012; 36: 963–8.
24. Jiang MH, Yang Y, Guo XF, Sun YX. Association between child and adolescent obesity and parental weight status: a cross-sectional study from rural North China. J Int Med Res 2013; 41:1326–32.

25. Bryant M, Stevens J, Wang l, Tabak R, Borja J, Bentley ME. Relationship between home fruit and vegetable availability and infant and maternal dietary intake in African American families: evidence from the exhaustive home food inventory. J Am Diet Assoc 2011; 111: 1491–7.
26. Pearson N, Biddle SJH, Gorely T. Family correlates of fruit and vegetable consumption in children and adolescents: a systematic review. Public Health Nutr 2009; 12: 267–83.
27. Ward DS, Vaughn AE, Bangdiwala SI, Campbell Jones AJ, Panter AT, Stevens J. Integrating a family-focused approach into child obesity prevention: rationale and design for the my parenting SOS study randomized control trial. BMC Public Health 2011; 11: 1–9.
28. Tang D, Bu T, Dong X. Are parental dietary patterns associated with children's overweight and obesity in China?. BMC Pediatrics 2020; 20: 12.
29. Bortolini GA, Gubert MB, Santos LM. Food consumption in Brazilian children by 6 to 59 months of age. Cad Saude Publica 2012; 28: 1759-71.
30. Quaioti TC, Almeida SS. Determinantes psicobiológicos do comportamento alimentar: uma ênfase em fatores ambientais que contribuem para a obesidade. Psicol USP 2006; 17: 193-211.
31. Coon KA, Tucker KL. Television and children's consumption patterns. A review of the literature. Minerva Pediatr 2002; 54: 423–36.
32. Dennison BA, Erb TA, Jenkins PL. Television viewing and television in bedroom associated with overweight risk among low-income preschool children. Pediatrics 2002; 109: 1028–35.

Original Article

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Does radiographic evaluation pulmonary edema score predict intensive care admission in COVID-19 patients presenting to the emergency department? A retrospective single-center observational study

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ABSTRACT

Aim: COVID-19 disease can progress from pneumonia to acute respiratory distress syndrome (ARDS). Performing computed tomography on all patients is expensive and exposes them to high radiation. The simple and reproducible Radiographic Evaluation Pulmonary Edema (RALE) score, used in ARDS and acute pulmonary edema in the emergency department, can predict the severity of the disease in COVID-19 patients.

Material and Method: In our study, a total of 221 COVID-19 patients we followed up between July-November, 2021 were evaluated retrospectively. The patients were divided into two as Intensive care hospitalization and no intensive care hospitalization.

Results: Ninety-five (43%) patients were admitted to the intensive care unit. The mean age (p<.001), white blood cell count (WBC) (p=.001), neutrophil count (p<.001), RALE score, and the number of hospitalization days of the patients admitted to the intensive care unit were higher (p<.001). These findings were positively correlated with the RALE score (p<.001). Age (p<.001), RALE score (p=.022), WBC (p=.029), and neutrophil count (p=.004) were independent risk factors in the multivariate analysis of factors affecting intensive care admission. RALE score cut-off value in predicting intensive care unit admission was ≥10.5. In the analysis with an Area Under the Curve value of 0.716, the application of this threshold resulted in a sensitivity of 67.4% and a specificity of 69.8%.

Conclusion: In conclusion, performing chest computed tomography in all patients admitted to the emergency department with COVID-19 disease increases the cost and exposure to radiation. The simple and recalculated RALE score can be used to predict intensive care admission in COVID-19 pneumonia.

Keywords: COVID-19, RALE, intensive care unit, emergency department

INTRODUCTION

At the end of 2019, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus was first observed in China. This new coronavirus has caused a highly contagious disease called Coronavirus Disease 19 (COVID-19). It can progress from lung infection to acute respiratory distress syndrome (ARDS)(1, 2). The genetic sequencing of SARS-CoV-2, real-time reverse transcription-polymerase chain reaction (RT-PCR) of viral nucleic acid is the gold standard for the diagnosis(1). However, this serological examination has limitations due to its high number of false negatives and delayed diagnosis. Especially in the emergency room, to be able to quickly evaluate the radiological thoracic involvement of patients with suspected COVID-19, the computed tomography (CT) findings are focused on first, which are more sensitive and specific rather than chest CXR. CT has been used as the primary diagnostic method for COVID-19 in China (3, 4). In addition, it should be kept in mind that CT scanning during the pandemic is not suitable as a primary imaging method, given the excessive radiation exposure and the mandatory disinfection procedures that must be performed. Most Italian hospitals use CXR as a primary

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method with portable X-ray units, which reduce the mobility of patients and minimize the risk of cross-infection (4-7). Previously, it was determined that there was a relationship between RALE scoring and oxygenation of patients with ARDS and disease severity. In a study, the high RALE score calculated by chest X-ray of patients admitted to the emergency room due to COVID-19 predicted admission to the intensive care unit (ICU) (8). RALE score, which may be associated with an increased risk of ICU admission, can be used as a quantitative measure of the COVID-19 pneumonia severity in emergency cases, as it is a simple and reproducible measure. It can help identify the highest-risk patients and allow timely initiation of currently available treatments against COVID-19 (9).

The primary aim of our study was to demonstrate that the RALE score calculated according to the safe and inexpensive CXR can predict ICU admission in patients with COVID-19. We suggested that the use of computed tomography, which is expensive and causes radiation exposure, can be reduced by evaluating the power of the RALE score in predicting ICU admissions.

MATERIAL AND METHOD

The study was conducted with the permission of the Non-invasive Clinical Education Planning Board of 3rd step Training and Research Hospital in Kayseri (Date: 17.06.2021 Decision No: 414). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The present study retrospectively evaluated COVID-19 patients who applied to the emergency department and who were hospitalized between July 01 and November 01, 2021.

Patients with RT-PCR positive results, who had chest x-rays in the emergency room or on the first day of hospitalization, were included in the study. Patients with lung/other malignancy, heart failure, acute/chronic renal failure, acute/chronic liver failure were excluded. A score of 0-4 was assigned to each lung depending on the extent of involvement by consolidation (0 = no involvement; 1 = <25%; 2 = 25-50%; 3 = 50-75%; 4 = >75% involvement). The scores for each lung were summed to produce the final RALE score.

In addition to viral pneumonia, patients' demographic data (age, BMI, gender), comorbidities, RALE scores, intensive care unit admissions, total hospitalization days, laboratory parameters (first-day C-reactive protein (CRP), procalcitonin, white blood cell (WBC), neutrophils, lymphocyte, platelet, ferritin, fibrinogen), acute pathologies in the lung (pneumothorax, pleural effusion, pulmonary embolism) were recorded.

All CXRs were obtained as digital radiographs in the isolation wards of our emergency department in the same portable X-ray unit (C50 Digital X-Ray system, Philips, Nederland). CXRs were generated in the rear-front or front-rear projection. All images were recorded in the hospital patient registry program. A chest radiologist and an intensive care specialist did the retrospective examination of each CXR. Thorax tomography was performed in all patients. In PCR-positive patients, radiographic findings (with thorax tomography), including pneumonia and consolidation, ground-glass opacities (GGO), pulmonary nodules, and reticular-nodular opacities, were diagnosed according to the Fleischer Society glossary of terms (10). CXRs were evaluated for the presence of distribution in the infiltration (mostly peripheral/perihilar, unilateral/bilateral, inferior/superior/diffuse). Other pulmonary pathological thoracic images were also evaluated (cardiomegaly, hilar vascular congestion, pleural effusion, pneumothorax). A severity scoring was applied to measure the extent of COVID-19 pulmonary involvement RALE. Following RALE indications, each CXR was assigned with a score ranging from 0 to 48. 0 points were given in the absence of any pathological findings and 48 points in the complete pathological involvement of the lung parenchyma. A score of 0-4 was assigned to each lung depending on the extent of involvement by consolidation (0 = no involvement; 1 = <25%; 2 = 25-50%; 3 = 50-75%; 4 = >75% involvement). The scores for each lung were summed to produce the final RALE score.

The RALE score, which was calculated by two people from the study team, was recorded with the common opinion of the two.

The patients were divided into two groups: intensive care hospitalization and no intensive care hospitalization. The demographic and clinical characteristics of the patients were compared between these two groups. The relationship between the RALE score and the independent risk factors predicting admission to the intensive care unit was determined.

Statistical Analysis

Statistical analysis of the data obtained in the study was performed using statistical package for social sciences (SPSS) version 22.0 software. Continuous variables were expressed as median value and interquartile range (IQR). On the other hand, categorical variables were presented as numbers (n) and percentages (%). The continuous variables were compared using analysis of variance (ANOVA) or Mann-Whitney U test (Kolmogorov–Smirnov test) according to whether the data were suitable for normal distribution. ROC

analysis was performed to determine the cut-off value for the RALE score. The correlation between the RALE score and the factors determining admission to the intensive care unit was examined using Spearman's correlations.

A forward-step binary logistic regression analysis was performed to determine the independent factors predicting admission to the ICU. The variables were determined as p-value <0.1 in univariate analysis, and the results were presented with the odds ratio (OR) and Confidence interval (CI).

RESULTS

For the study, the files of 300 patients who were hospitalized were evaluated retrospectively. Among all patients, 19 were excluded due to acute renal failure, 25 for chronic renal failure, 11 for cirrhosis, 14 for malignancy, and 10 for heart failure.

Of the 221 patients included in the study, 95 (43%) were admitted to the ICU. The patients were evaluated in two groups according to their admission to the ICU. The demographic and clinical characteristics of the patients in the two groups are compared in **Table 1**.

Table 1. Demographic and clinical characteristics according to patients' admission to the intensive care unit

Variables	General (n:221)	Intensive care hospitalization (n:95)	No intensive care hospitalization (n:126)	P value
Age, year	62 (53-72	71 (62-82)	60 (49.75-63)	<.001
Body mass index	28 (25-32)	28.5 (22-36,5)	28 (26-32)	.555
Female/male	117/104 (53/4)	43/51 (45/55)	73/53 (42/58)	.087
Diabetes mellitus	119 (54)	38 (40)	81 (64)	<.001
Hypertension	111 (50)	48 (51)	63 (50)	.938
Chronic obstructive pulmonary disease	46 (21)	18 (19)	28 (20)	.682
Coronary artery disease	40 (18)	24 (25)	16 (13)	.529
Cerebrovascular disease	11 (5)	7 (7)	4 (3)	.157
Distribution				.684
Peripheral	179 (81)	76 (80)	103 (82)	
Perihilar	4 (2)	1 (1)	3 (2)	
Basal predominance	31 (14)	15 (16)	16 (13)	
Superior predominance	5 (2)	2 (2)	3 (2)	
Diffuse	2 (1)	1 (1)	1 (1)	
Lung involvement				.686
Unilateral	8 (4)	4 (3)	4 (3)	
Bilateral	213 (96)	91 (96)	122 (97)	
Pulmonary embolism	5 (2)	4 (3)	1 (1)	.09
Pneumothorax	1 (1)	1 (1)	0 (0)	.385
Pleural effusion	8 (3)	8 (8)	0 (0)	.001
Mechanical				<.001
Ventilation(MV)support	46 (21)	46 (48)	0 (0)	
Invasive MV support	34 (15)	34 (36)	0 (0)	
Noninvasive MV support	28 (13)	28 (29)	0 (0)	
Reservoir mask	69 (31)	55 (57)	14 (11)	<.001
Nasal oxygen	173 (78)	47 (49)	126 (100)	<.001
White blood cell count, $\times10^3$/L,	8.48 (5.9-12.9)	10.8 (7.4-14.2)	6.85 (5.25-9.72)	.001
Lymphocyte count, $\times10^3$/L	1.09 (0.62-1.74)	0.71 (0.49-1.2)	1.3 (0.89-1.95)	.740
Neutrophil count, $\times10^3$/L	5 (3.38-9.93)	8.87 (5.84-12.46)	3.65 (2.95-5.41)	<.001
Platelets, $\times10^3$/L, (median)	234 (178-297)	235 (163-293)	231 (187.25-310.25)	.541
C-reactive protein, mg/L	49.5 (15.75-110	91 (49.2-143)	28.5 (8.97-66.52)	<.001
Procalcitonin, ng/ml	0.13 (0.07-0.54)	0.3 (0.11-1.07)	0.09 (0.05-0.21)	.230
Serum ferritin, ng/ml	355 (160-794)	567 (267.5-1226)	208 (111-554.5)	.012
Serum fibrinojen, ng/ml	5410 (4510-6500)	5505 (4460-6767.5)	5360 (4520-6380)	.707
Hospital stay, day	11 (7-17)	15 (9-23)	9 (7-13)	<.001
RALE score	10 (6.5-16)	14 (9-20)	8 (6-12)	<.001

The median age of patients hospitalized in the intensive care unit was 71 years (62-82), and of patients not hospitalized in the intensive care unit was 57 (50-64) (p <.001).

WBC (10.8[7.4-14.2] vs. 6.85[5.25-9.72]x103/L) and neutrophil (8.8 [5.8-12.46] vs. 3.65[2.95-5.41] x103/L) counts were higher in ICU hospitalized patients compared to the other group (p=.001). CRP (91[49.2-143] vs. 28.5[8.97-66.52] mg/L, p=.001) and ferritin (567[267.5-1226] vs. 208[111-554.5] ng/ml, p=.012) levels were higher ICU patients.

At the same time, total duration of hospital stay (15 [9-23] vs. 9[7-13] days p<.001) and RALE scores (14 [9-20] vs. 8[6-12] p<.001) were higher in those admitted to the ICU.

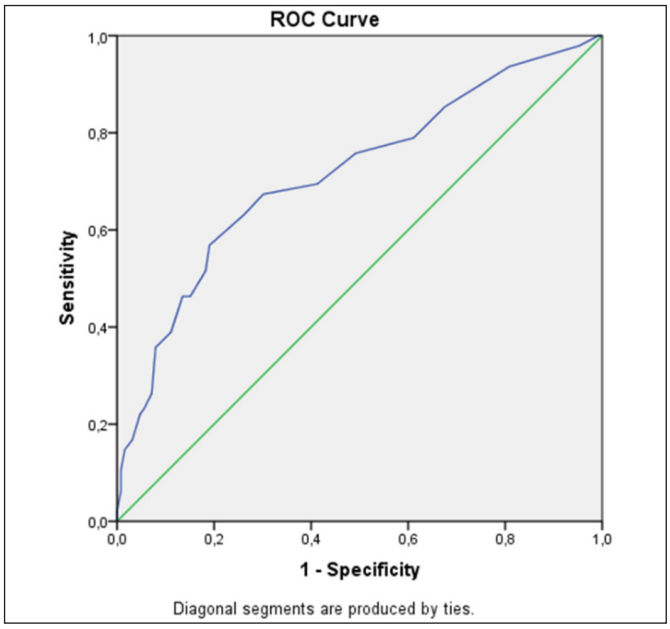
WBC, neutrophil, CRP, number of days of hospitalization, and RALE score, which was higher in patients admitted to the ICU, showed a positive correlation (**Table 2**). As the RALE score increased, CRP and number of hospitalization days increased.

Age (p<.001), RALE score (p=.022), WBC (p=.029), and neutrophil count (p=.004) were independent risk factors in the multivariate analysis of factors affecting intensive care admission (**Table 3**).

Table 3. Multivariate analysis of factors affecting intensive care admission

	p	OR	95% C.I.for EXP(B)	
			Lower	Upper
Age	<.001	1.085	1.046	1.125
RALE	.022	1.114	1.015	1.222
WBC	.029	1.141	1.013	1.285
Neutrophil	.004	1.239	1.072	1.433
CRP	.412	1.004	.998	1.013
Hospital stay	.075	1.051	.995	1.111

ROC analysis for the RALE score was performed to evaluate its success in predicting admissions to the intensive care unit. RALE score cut-off value in predicting intensive care unit admission was ≥10.5. In the analysis with an AUC value of 0.716, the application of this threshold resulted in a sensitivity of 67.4% and a specificity of 69.8%. The ROC curve showing the diagnostic performance in predicting ICU admission is presented in a graph (**Figure 1**).



Risk Factor	AUC (%95)	Cut Off	Sensitivity	Specificity
RALE	0.716	10.5	67.4	69.8

Figure 1. ROC curve RALE score

DISCUSSION

This study evaluated the parameters used to predict ICU admission in COVID-19 pneumonia and revealed that the RALE score was associated with these parameters. In the study, the RALE score was calculated by evaluating the chest x-rays taken in the emergency room of 221 patients who applied with the symptoms of COVID-19 and had positive PCR test results. The patients were divided into two groups according to their intensive care hospitalization status. Patients admitted to the intensive care unit were determined to be older and had higher white blood cell and neutrophil counts, CRP levels, number of hospitalization days, and RALE scores. When the correlation of these parameters indicating admission to the intensive care unit was examined, all parameters showed a positive correlation with the RALE score. Patients with a high RALE score in the beginning also had higher hospitalization days. RALE score cut-off value in predicting intensive care unit admission was ≥10.5. In the analysis with an AUC value of 0.716, the application of this threshold resulted in a sensitivity of 67.4% and a specificity of 69.8%. In recent studies, COVID-19 chest computed tomography examination has been discussed, and its sensitivity has been reported as 98% (11-13).

Table 2. Correlation of RALE score and factors affecting intensive care admission

	RALE		CRP		Hospital stay		WBC		Neutrophil	
	r	p	r	p	r	p	r	p	r	p
RALE	1	NS	0.572	<0.001	0.331	<0.001	0.144	0.032	0.343	<0.001
WBC	0.144	0.032	0.170	0.011	0.000	0.997	1	NS	0.413	<0.001
Neutrophil	0.343	<0.001	0.473	<0.001	0.124	0.066	0.413	<0.001	1	NS
CRP	0.572	<0.001	1	NS	0.184	0.006	0.170	0.011	0.473	<0.001
Hospital stay	0.331	<0.001	0.184	0.006	1	NS	0.000	0.997	0.124	0.066

Although CXR has less sensitivity than CT, it is less expensive and contains less radiation.

Due to the pandemic experienced worldwide, rapid determination of the radiological diagnosis of patients with suspected COVID-19 infection is vital for the most efficient operation of the emergency department. While CXR is the primary imaging tool, the typical features of COVID-19 pneumonia are defined by chest CT in selected cases (5, 6). Many recent studies have reported that CXR does not have the diagnostic power of CT but has a crucial role as a primary examination in managing the pandemic (5, 13, 14). Although CT has a high sensitivity (approximately 97–98%) in detecting typical characteristics of COVID-19 pneumonia, it has low specificity (13-15). RALE score higher than 15 is associated with an increased risk of admission to the intensive care unit. It is stated that the RALE score can be used in an emergency (8).

In a study, advanced age, comorbidities, RALE score, and biomarkers of systemic hyperinflammation (i.e., Lymphopenia below 0.9 x 103/L, high LDH, and high D-dimer) were determined as predictors of early death in COVID-19 pneumonia (16). In our study, age, WBC, neutrophils, CRP, and the number of days of hospitalization affected the number of days of COVID-19 pneumonia. A very recently published study indicated that inflammatory markers and RALE scores were correlated in COVID-19 patients (17).

In the initial patient evaluation in the emergency department, the RALE score seems like a simple tool to predict clinical outcomes quite early.

There are multiple potential applications for the RALE score for both patient care and clinical research in patients with ARDS. RALE scores can be used to clinically identify patients at the highest risk of mortality, leading to earlier detection and intervention of high-risked patients with ARDS. It has been stated that a similar approach can be used for the therapeutic risk classification of ARDS patients (9). In this study, we have statistically demonstrated that the RALE score predicts the severity of COVID-19 pneumonia and the indication for hospitalization in the intensive care unit.

Both computed axial tomography and ultrasound have been used to evaluate the presence and distribution of pulmonary edema (18). However, none are as practical as RALE scoring for daily assessment. Sensusiati et al.(19). stated that there was a strong correlation between the risk of death in hospitalized COVID-19 patients and the RALE score and that the RALE score could be used as a predictor of mortality in COVID-19 patients. Considering that hospitalization in the intensive care unit for COVID-19 disease determines the risk of mortality, the factors affecting the hospitalization of the patients to the intensive care unit also affect mortality.

In our study, admission to the intensive care unit was affected independently by age, WBC, neutrophil, CRP, and RALE scores. However, since the sensitivity specificity of the RALE score is not very high, its use may be more limited.

The retrospective nature of the study and the inability to detect mortality results can be considered among the limitations of our study. Our other limitations are that we could not compare the patients with non-COVID-19 patient groups, and could not examine the effect of comorbidity conditions on the RALE score.

CONCLUSION

It suggests that the simple and recalculated RALE score can be used to show the severity and prognosis of COVID-19 pneumonia in the first place..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of the Non-invasive Clinical Education Planning Board of 3rd step Training and Research Hospital in Kayseri. (Date: 17.06.2021 Decision No: 414).

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

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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. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020; 470-3.
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. Yang W, Sirajuddin A, Zhang X, et al. The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). Eur Radiol 2020; 30: 4874-82.
4. Zhou S, Wang Y, Zhu T, Xia L. CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. AJR Am J Roentgenol 2020; 214: 1287-94.
5. Giovagnoni A. Facing the COVID-19 emergency: we can and we do. Radiol Med 2020; 125: 337-8.

6. Neri E, Miele V, Coppola F, Grassi R. Use of CT and artificial intelligence in suspected or COVID-19 positive patients: statement of the Italian Society of Medical and Interventional Radiology. Radiol Med 2020; 125: 505-8.
7. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. American College of Radiology. March 11, 2020.
8. Cozzi D, Albanesi M, Cavigli E, et al. Chest X-ray in new coronavirus disease 2019 (COVID-19) infection: findings and correlation with clinical outcome. Radiol Med 2020; 125: 730-7.
9. Warren MA, Zhao Z, Koyama T, et al. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. Thorax 2018; 73: 840-6.
10. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008; 246: 697-722.
11. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical coronavirus disease 2019 (COVID-19) pneumonia: relationship to negative RT-PCR testing. Radiology 2020; 296: E41-E5.
12. Huang P, Liu T, Huang L, et al. Use of Chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology 2020; 295: 22-3.
13. Fang Y, Zhang H, Xie J, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology 2020; 296: E115-E7.
14. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020; 296: E32-E40.
15. Choi H, Qi X, Yoon SH, et al. Extension of coronavirus disease 2019 on chest CT and Implications for chest radiographic ınterpretation. Radiol Cardiothorac Imaging 2020; 2: e200107.
16. Ciceri F, Castagna A, Rovere-Querini P, et al. Early predictors of clinical outcomes of COVID-19 outbreak in Milan, Italy. Clin Immunol 2020; 217: 108509.
17. Marques P, Fernandez-Presa L, Carretero A, et al. The radiographic assessment of lung edema score of lung edema severity correlates with inflammatory parameters in patients with coronavirus disease 2019-Potential new admission biomarkers to predict coronavirus disease 2019 worsening. Front Med 2022; 9: 871714.
18. Bellani G, Rouby JJ, Constantin JM, Pesenti A. Looking closer at acute respiratory distress syndrome: the role of advanced imaging techniques. Curr Opin Crit Care 2017; 23: 30-7.
19. Sensusiati AD, Amin M, Nasronudin N, et al. Age, neutrophil lymphocyte ratio, and radiographic assessment of the quantity of lung edema (RALE) score to predict in-hospital mortality in COVID-19 patients: a retrospective study. F1000Res 2020; 9: 1286.

Original Article

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Evaluation of the safety and antiviral efficacy of the tenofovir alafenamide fumarate molecule in immunosuppressed patients

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ABSTRACT

Aim: Patients with chronic or prior hepatitis B virus (HBV) infection may experience HBV reactivation during immunosuppressive therapy. The objective of this study was to evaluate the safety and antiviral efficacy of tenofovir alafenamide fumarate (TAF) for prophylaxis of HBV reactivation in patients on immunosuppressive therapy.

Material and Method: This study included patients who were started on immunosuppressive treatment due to hematologic/solid malignancy, autoimmune disease, or inflammatory disease and were treated with TAF for at least six months due to HBsAg and/or total anti-HBc positivity at Karadeniz Technical University Farabi Hospital between January 2018 and February 2021. Electronic medical records were retrospectively reviewed and the adverse event profile was analyzed.

Results: Of the 94 patients enrolled in the study, 70.2% (n=66) were male. The mean age of the patients was 60.37±14.56 years. The reasons for initiation of immunosuppressive drug treatment were hematologic malignancies in 48.9% (n=46), solid tumors in 27.7% (n=26), and other causes (autoimmune/inflammatory) in 23.4% (n=22). There was no statistically significant difference in creatinine, phosphorus, glucose, and LDL profile between baseline and 6-12 months of TAF treatment (p=0.861, p=0.136, p=0.323, p=0.304, respectively). All patients in whom HBV DNA was detectable at baseline became negative at the last follow-up visit. None of the patients developed HBV reactivation and there was no need to discontinue antiviral/immunosuppressive treatment due to side effects.

Conclusion: TAF is a safe and effective short-term option to prevent HBV reactivation in patients receiving immunosuppressive therapy.

Keywords: Hepatitis B, chronic hepatitis B, reactivation, tenofovir alafenamide, chemotherapy, immunosuppression

INTRODUCTION

The Hepatitis B virus (HBV) is a DNA virus that can cause acute/chronic hepatitis, liver failure, liver cancer (HCC), and even death. It has infected more than 2 billion people worldwide, about 400 million of whom have a chronic disease (1,2). Our country is one of the endemic regions at intermediate risk for HBV infection. According to the TURHEP study, the positivity rate for hepatitis B virus surface antigen (HBsAg) was 4% and the positivity rate for hepatitis B core protein antibody (anti-HBc total) was 31% (3).

HBV reactivation may develop in patients with chronic or previous hepatitis B infection during immunosuppressive treatment. Reactivation is characterized by the sudden relapse or elevation of HBV DNA in a patient with previously inactive or disappeared HBV infection. Especially in patients who receive rituximab-based chemotherapy and undergo bone marrow/stem cell transplantation, the reactivation rate can be up to 88% (4-6).

Depending on the efficacy of immunosuppressants and overall HBs-Ag and/or anti-HBc total positivity, the risk of HBV reactivation is classified as high risk (> 10%), intermediate risk (1%-10%), and low risk (< 1%) (7).

The molecules entekavir and tenofovir are oral antiviral drugs recommended as the first-line treatment for HBV due to their high efficacy (8). Tenofovir has two different molecules: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF). It is known that long-term use of TDF may cause a decrease in bone

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mineral density and renal toxicity (9). For these reasons, switching from TDF to TAF or entecavir is recommended in patients who receive long-term antiviral treatment (10,11), and treatment with TAF is recommended in immunosuppressive patients at high risk for bone and renal side effects (12).

The objective of this study was to evaluate the short-term safety and antiviral efficacy of the TAF molecule in immunosuppressed patients.

MATERIAL AND METHOD

The study was conducted with the permission of Karadeniz Technical University Faculty of Medicine Scientific Researches Ethics Committee (Date: 24.11.2021, Decision No: 24237859-850). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Since this was a retrospective study, informed consent was not obtained from the patients.

Study Design

This study included patients over 18 years of age who initiated immunosuppressive treatment for hematologic/solid malignancy, autoimmune disease, or inflammatory disease, were found to be HBs-Ag or anti-HBc total positive, started TAF treatment, and had at least six months of treatment and follow-up between January 2018 and February 2021 at Karadeniz Technical University Farabi Hospital (**Figure 1**).

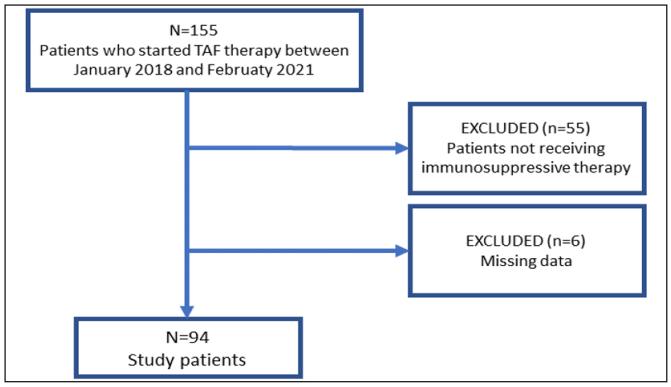

Figure 1. Flow chart of the patients included in the study

Age, sex, body mass index (BMI) (kg/m²), chronic diseases, reason for immunosuppressive treatment, HBV seroprofile (HBs Ag, anti-HBs, HBe, anti-HBe, HBV DNA), creatinine (mg/dL), phosphorus (mg/dL), Data for lipid profile (low density lipoprotein (LDL) (mg/dL), triglycerides (mg/dL), high density lipoprotein (HDL) (mg/dL)) were obtained retrospectively from the hospital electronic data archive. For laboratory tests, baseline values and final values at 6-12 months were recorded. HBV DNA was analyzed by PCR and reported in units of IU/mL.

HBV reactivation was defined as a positive HBV DNA level, a positive HBV DNA level when Hbs-Ag was negative, or a ≥1 log10 increase in baseline HBV DNA level.

Based on immunosuppressive treatment and HBV serology, HBV reactivation risk has been classified as high (> 10%), intermediate (1-10%), and low risk (< 1%) according to the recommendations of the Asian Pacific Association for the Study of Liver (APASL) (7).

Statistical Analysis

The SPSS Windows version 22 program was used for statistical tests. Continuous variables were analyzed by the histogram or Q-Q plot in terms of normal distribution and Shapiro-Wilk or Kolmogorov-Smirnov tests depending on the number of variables. We presented normally distributed continuous variables throughout the study as mean±standard deviation, and the t-test for independent variables was used to compare the two groups. Other continuous variables were presented as median (minimum-maximum), and the nonparametric Mann-Whitney U test was used to compare the groups. We presented categorical variables as frequencies and percentages and used the Pearson chi-square test or Fischer's exact probability test to compare the groups. Tests with a p-value of 0.05 or less at the 95 percent confidence interval were considered statistically significant.

RESULTS

The study included 94 patients. 70.2% (n=66) were male and 29.8% (n=28) were female. The mean age of the patients was 60.37±14.56 years. There was no significant difference between men and women in terms of age (p=0.606). Patients' mean BMI was 26.83±5.74 and no significant difference was found between men and women in terms of BMI (p=0.372) (**Table 1**).

Table 1. Demographic characteristics of the patients

Variable		p
Male / Female, n (%)	66 (70.2) / 28 (29.8)	
Age, mean±SD	60.37±14.56	0.606
Male	59.86±14.99	
Female	61.57±13.65	
BMI, mean±SD	26.83±5.74	0.372
Male	26.42±5.61	
Female	27.80±6.06	

*BMI: Body Mass Index

The comorbidities of the patients were as follows: Hypertension in 40.4% of patients (n=38), diabetes mellitus in 23.4% (n=22), chronic renal failure in 19.1% (n=18), coronary artery disease in 10.6% (n=10), osteoporosis in 7.4% (n=7).

Hematologic malignancies ranked first among causes of immunosuppressive drug treatment with a rate of 48.9% (n=46). Immunosuppressive drug treatment was initiated for solid tumors in 27.7% of patients (n=26) and for other reasons (autoimmune/inflammatory diseases) in 23.4% of patients (**Figure 2**).

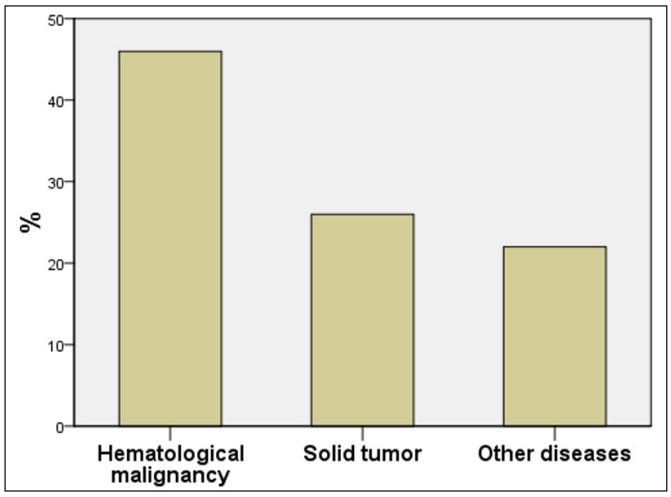

Figure 2. Reasons for initiating immunosuppressive drug treatment

When patients' hepatitis B seroprofiles were analyzed, 24.5% (n=23) were HBs-Ag positive, 75.5% (n=71) were HBs-Ag negative and anti-Hbc total positive.

6.4% (n=6) of patients received antiviral treatment before TAF treatment (one patient with lamivudine, two patients with entecavir, and the remaining three patients with tenofovir disoproxil fumarate). TAF treatment was initiated in two patients because of hypophosphatemia, in one patient because of a GFR <of 60 ml/min/1.73 m², in one patient due to the use of drugs affecting bone mineral density, and in two patients due to the preference of the physician.

Regarding HBV reactivation, 33% (n=31) of patients were at low risk, 42.6% (n=40) were at intermediate risk, and 24.5% (n=23) were at high risk.

When we analyzed serum creatinine (p=0.861), phosphorus (p=0.136), glucose (p=0.323), total cholesterol, LDL, HDL, and triglyceride levels at baseline and after 6-12 months of TAF treatment, no statistically significant difference was found (p>0.05) (**Table 2**).

Table 2. Patients' baseline and most recent laboratory values at follow-up

Variable, mean±SD	Baseline	Most recent	p
Glucose, n=47	120.59±46.76	115.98±42.3	0.323
Creatinine, n=59	0.93±0.43	0.87±0.28	0.861
Phosphorus, n=45	3.49±0.83	3.31±0.71	0.136
Total cholesterol, n=11	215.36±51.21	237.64±81.59	0.262
LDL, n=11	138.82±45.28	156.73±64.22	0.304
HDL, n=12	57.92±29	51.5±15.4	0.402
Triglycerides, n=12	149.42±68.14	196.33±152.293	0.363

*LDL: Low dansity lipoprotein, HDL: High dansity protein

All 17 patients with measurable HBV DNA values before treatment had negative HBV DNA values during follow-up after 6-12 months of TAF treatment. No patient developed hepatitis B reactivation.

Regarding the side effect profile, no patient had to discontinue antiviral treatment.

DISCUSSION

Our country is among the intermediate-risk regions in terms of HBV (3). HBV reactivation is a common complication in patients receiving immunosuppressive therapy and can be prevented by appropriate screening and treatment options (13).

The risk of HBV reactivation is classified into three groups based on HBV serology and immunosuppressive treatment received. HBV reactivation risk is classified as high risk if it is more than 10%, intermediate risk if it is between 1-10%, and low risk if it is <1% (7).

Although there are differences between guidelines, all guidelines recommend initiating prophylactic antiviral treatment in patients with a high risk of reactivation (7,10,12,14).

The American Association for the Study of Liver Diseases (AASLD), APASL, and the European Association for the Study of the Liver (EASL) recommend prophylactic antiviral therapy for all patients with chronic HBV infection, whereas the American Gastroenterological Association (AGA) recommends it only for high- and intermediate-risk patients. For patients with prior hepatitis B infection, the AASLD, APASL, AGA, and EASL recommend prophylactic antiviral therapy for high-risk patients, whereas initiation of antiviral therapy with follow-up is left to the physician's decision for intermediate-risk patients. In low-risk patients, prophylactic antiviral treatment is not recommended. Antiviral treatment should be initiated if HBV reactivation occurs or is suspected during follow-up (7,10,12,14). In the most recent update, the APASL recommends measurement of liver fibrosis in low-risk patients with chronic HBV infection and intermediate-risk patients with prior hepatitis B and recommends initiation of prophylactic antiviral treatment in patients with advanced fibrosis or cirrhosis (7).

In terms of HBV reactivation risk, 33% (n=31) of patients in our study had low risk and 67% (n=63) had moderate and high risk. Prophylactic antiviral treatment is initiated before immunosuppressive treatment to prevent treatment discontinuation after possible HBV reactivation even in low-risk patients and especially in those with hematologic malignancies, due to the late-acquired results of the HBV DNA test (14 days) in our

center and the possibility of treatment discontinuation during follow-up since patients' primary follow-up of HBV reactivation is performed by the clinic where immunosuppressive treatment is first initiated.

It is recommended to start HBV prophylaxis 1-3 weeks before immunosuppressive treatment or at least at the same time (7,10,15). In 48.9% of our patients (n=46), antiviral prophylaxis was initiated before or with immunosuppressive treatment.

Many guidelines recommend entecavir and tenofovir molecules instead of lamivudine for prophylactic antiviral treatment because of their high efficacy and genetic barriers. Yang et al. (16) showed that the risk of HBV reactivation was lower in patients using entecavir, and Picardi et al. (17) showed that the risk of HBV reactivation was lower in patients using tenofovir disoproxil (TDF) compared with lamivudine.

In the literature, TDF use has been associated with decreased renal function and bone mineral density (18,19). Compared with TDF, TAF may produce effects at lower doses because of its high plasma stability and longer plasma life (20,21). It is recommended to use TAF or entecavir instead of TDF in patients at high risk for bone or renal side effects (10,11,22). In our study, consistent with the literature, there was no worsening of patients' renal functions (creatinine and phosphorus levels) (p=0.861 and p=0.136, respectively).

Although the mechanism is unclear, an association between TDF and a decrease in lipid levels has been reported in several studies (23-25). In a study conducted by Malloon et al. (26) examining the lipid profile of patients who were switched from TDF to TAF, an increase in LDL and triglyceride levels was observed after 9-16 months. In our study, an increase in total cholesterol, LDL and triglyceride levels and a decrease in HDL levels were found in patients whose lipid profile was monitored, but no statistically significant difference was found (p>0.05).

Squillace et al. (27) found an increase in glucose levels in patients who were switched from TDF to TAF, and Li et al. (28) found an increase in glucose levels in patients who were switched from entecavir to TAF. In our study, although there was a decrease in patients with glucose monitoring, it was not statistically significant (p=0.323).

The main limitations of our study are that it was a single center and that some of the patients were followed up for HBV reactivation by the clinic where the immunosuppressive treatment was started. Since there are few studies in the literature that include patients receiving immunosuppressive therapy and using antiviral therapy TAF, multicenter prospective studies are needed.

CONCLUSION

TAF is a safe and effective option for preventing HBV reactivation in patients receiving immunosuppressive therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of Karadeniz Technical University Faculty of Medicine Scientific Researches Ethics Committee (Date: 24.11.2021, Decision No: 24237859-850).

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. Kawsar HI, Shahnewaz J, Gopalakrishna K v, Spiro TP, Daw HA. Hepatitis B reactivation in cancer patients: role of prechemotherapy screening and antiviral prophylaxis. Clin Adv Hematol Oncol 2012; 10: 370-8.
2. Pattullo V. Hepatitis B reactivation in the setting of chemotherapy and immunosuppression-prevention is better than cure. World J Hepatol 2015; 7: 954-67.
3. Tozun N, Ozdogan O, Cakaloglu Y, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect 2015; 21: 1020-6.
4. Ling WHY, Soe PP, Pang ASL, Lee SC. Hepatitis B virus reactivation risk varies with different chemotherapy regimens commonly used in solid tumours. Br J Cancer 2013; 108: 1931-5.
5. Lau GK, Liang R, Chiu EK, Lee CK, Lam SK. Hepatic events after bone marrow transplantation in patients with hepatitis B infection: a case controlled study. Bone Marrow Transplant 1997; 19: 795-9.
6. Dai MS, Wu PF, Shyu RY, Lu JJ, Chao TY. Hepatitis B virus reactivation in breast cancer patients undergoing cytotoxic chemotherapy and the role of preemptive lamivudine administration. Liver Int 2004; 24: 540-6.
7. Lau G, Yu ML, Wong G, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. Hepatol Int. 2021; 15: 1031-48.
8. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018; 68: 672-81.
9. Casado JL. Renal and bone toxicity with the use of tenofovir: understanding at the end. AIDS Rev [Internet] 2016; 18: 59-68.
10. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67: 370-98.

11. Gill US, Zissimopoulos A, Al-Shamma S, et al. Assessment of bone mineral density in tenofovir-treated patients with chronic hepatitis B: can the fracture risk assessment tool identify those at greatest risk? J Infect Dis 2015; 211: 374-82.
12. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67: 1560-99.
13. Aygen B, Demir AM, Gumus M, et al. Immunosuppressive therapy and the risk of hepatitis B reactivation: Consensus report. Turk J Gastroenterol 2018; 29; 259-69.
14. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT, American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015; 148: 215-9; quiz e16-7.
15. Hwang JP, Somerfield MR, Alston-Johnson DE, et al. Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update. J Clin Oncol 2015; 33: 2212-20.
16. Yang C, Qin B, Yuan Z, Chen L, Zhou HY. Meta-analysis of prophylactic entecavir or lamivudine against hepatitis B virus reactivation. Ann Hepatol 15: 501-11.
17. Picardi M, della Pepa R, Giordano C, et al. Tenofovir vs lamivudine for the prevention of hepatitis B virus reactivation in advanced-stage DLBCL. Blood 2019; 133: 498-501.
18. Sax PE, Gallant JE, Klotman PE. Renal safety of tenofovir disoproxil fumarate. AIDS Read 2007; 17: 90-2, 99-104, C3.
19. Gallant JE, Winston JA, DeJesus E, et al. The 3-year renal safety of a tenofovir disoproxil fumarate vs. a thymidine analogue-containing regimen in antiretroviral-naive patients. AIDS. 2008; 22: 2155-63.
20. Ray AS, Fordyce MW, Hitchcock MJM. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. Antiviral Res 2016; 125: 63-70.
21. Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. J Hepatol 2015; 62: 533-40.
22. Chen YC, Su YC, Li CY, Hung SK. 13-year nationwide cohort study of chronic kidney disease risk among treatment-naïve patients with chronic hepatitis B in Taiwan. BMC Nephrol 2015; 16: 110.
23. Randell PA, Jackson AG, Zhong L, Yale K, Moyle GJ. The effect of tenofovir disoproxil fumarate on whole-body insulin sensitivity, lipids and adipokines in healthy volunteers. Antivir Ther 2010; 15: 227-33.
24. Santos JR, Saumoy M, Curran A, et al. The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. Clin Infect Dis 2015; 61: 403-8.
25. Shaheen AA, AlMattooq M, Yazdanfar S, et al. Tenofovir disoproxil fumarate significantly decreases serum lipoprotein levels compared with entecavir nucleos(t)ide analogue therapy in chronic hepatitis B carriers. Aliment Pharmacol Ther 2017; 46: 599-604.
26. Mallon PWG, Brunet L, Fusco JS, et al. Lipid changes after switch from TDF to TAF in the OPERA Cohort: LDL cholesterol and triglycerides. Open Forum Infect Dis 2022; 9: ofab621.
27. Squillace N, Ricci E, Menzaghi B, et al. The effect of switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) on liver enzymes, glucose, and lipid profile. Drug Des Devel Ther 2020; 14: 5515-20.
28. Li ZB, Li L, Niu XX, et al. Switching from entecavir to tenofovir alafenamide for chronic hepatitis B patients with low-level viraemia. Liver Int 2021; 41: 1254-64.

Original Article

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Evaluation of violence against emergency physicians

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ABSTRACT

Aim: To identify the causes of violence in the emergency department and suggest ways to reduce the violence experienced.

Material and Method: The population of this cross-sectional survey study consisted of all emergency medicine physicians who participated in the symposium on frequent emergencies held in Cyprus on May 6, 2022. The survey consisted of a total of 20 items comprising 16 multiple-choice and four fill-in-the-blank questions related to demographic characteristics and violence. It was administered to 230 physicians who volunteered to participate in the study.

Results: A total of 230 physicians, 65.2% (n=150) male and 34.8% (n=80) female, participated in the study. It was determined that 28.7% of the participants had been exposed to physical violence, 89.2% to verbal violence, and 1.3% to sexual violence within the last year. The factors causing violence were identified as the low educational level of patients' and their family members, patient requests for unnecessary medical practices, aggressive nature of family members, and patients' desire to be examined before their turn. As the number of shifts worked by the physicians and number of treated patients increased, the frequency of exposure to violence also increased. Women were exposed to more violence. As the title and age of the physicians increased, the frequency of exposure to violence decreased.

Conclusion: We consider that violence against physicians can be reduced by informing patients and patient's relatives and improving the working conditions of physicians.

Keywords: Healthcare workers, violence against physicians, emergency department

INTRODUCTION

The history of violence goes back as far as the history of humanity. Human history is deeply affected by highly violent events, such as wars that occur from time to time. These acts of violence sometimes reach a global level, affecting populations across the world, suggesting that as long as societies exist, violence will continue to exist. Violence is defined as all individual or social incidents that cause the impairment of the mental or physical integrity of people through force and oppression. According to the World Health Organization, violence refers to the intentional use of physical violence and the threat or actual use of force against oneself, another person, a group, or a community, which results in or is likely to result in injury, death, psychological harm, or loss (1).

Individuals working in the health system are 16 times more likely to be exposed to violence than the other sectors (2). A large number of violent incidents occur in emergency departments every day.These acts of violence consist of physical violence, verbal violence, and sexual assault. Despite all the measures taken, the incidence of violence hasnot decreased, and suchacts continue to adversely affect both healthcare workers and patients receiving healthcare (3). In a province-based study conducted on health workers in Turkey, it was determined that the most frequent place of violence was the emergency room with a rate of 70.6% (4).

Violence in emergency servicescannot be completely prevented due to numerous factors, including the number of presenting patients exceeding the capacity of the department, prolonged waiting time, unavailability of early outpatient clinic appointments, patients' being unwilling to wait, number of patients needed to be seen by an emergency physician being higher than ideal, lack of security measures, and many other reasons (5).

In this study, we aimed to determine the level of exposure to violence of doctors working in the emergency departments and the factors that may cause violence.

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MATERIAL AND METHOD

The study was conducted with the permission of University of Health Sciences Fatih Sultan Mehmet Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.04.2022, Decision No: 2022/7). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed asa cross-sectional survey. The population of this cross-sectional survey study consisted of all emergency medicine physicians who participated in the symposium on frequent emergencies held in Cyprus on May 6, 2022.

All data collection procedures were completed within one month after receiving approval from the ethics committee.The survey form consisted of two pages. It included a section questioning demographic characteristicsand 20 questions about the types of violence faced by emergency medicine physicians working in emergency departments and identify the causes of violence.The first fourquestions were in the form of fill-in-the-blanks questions, and the remaining 16 were prepared as multiple-choice questions. The meansurvey completion time was approximately 3 minutes.

Inclusion criteria were being actively working in an emergency department and agreeing to participate in the study. Physicians that did not activelysee patients, those that were not actively working in emergency departments, and those that were not voluntary to participate in the study were excluded.

The physicianswere verbally informed about the study and their consent was obtained. The survey was administered to the physicians by theresponsible and/or assistant researcher in an appropriate environment. The participants were not affected in any way.Survey forms with incomplete data were excluded.

The Number Cruncher Statistical System (NCSS) 2022 and Power Analysis and Sample Size (PASS) 2007 (Utah, USA) were used for statistical analyses. While analyzing the study data, in addition to descriptive statistics (mean, standard deviation, minimum, maximum, median, frequency, and ratio) in the comparison of quantitative data, Student's t-test was used for the two-group comparisons of normally distributed parameters and the Mann Whitney U test for those of non-normally distributed parameters. The Pearson chi-square and Yates continuity correction (Yates corrected chi-square) tests were undertaken to compare qualitative data. Significance was evaluated at the $p<0.01$ and $p<0.05$ levels.

RESULTS

A total of 230 emergency doctors (male 65.2%, mean age 32.63±5.6 years) were fulfilled the survey. The demographic characteristics including duration of employment, affiliations and the titles of the participants were presented in **Table 1**.

Table 1. The demographic characteristics of the participants

	Min-Max	Mean±SD
Age	24-55	32.63±5.60
Duration of working	1-31	5.33±5.26
	n	**%**
Gender		
Male	150	65.2
Female	80	34.8
Institution		
State Hospital	11	4.8
Training and Research Hospital	131	56.9
Medical Faculty	80	34.8
Special Hospital	8	3.5
Degree		
Research Assistant	134	58.3
Specialist	77	33.4
General Practitioner	3	1.3
Others	16	7.0

Physicians participating in the study reported that they were exposed to violence most frequently in the green area (44.3%) and yellow area (39.1%) of the emergency service, respectively. The most frequent attackers were relatives of the patients (96.9%, n=223), followed by patients (2.2%, n=5) and others (0.9%, n=2).

Of the participants, 28.7% (n=66) had been exposed to physical violence on duty within the last. Verbal violence on duty within the last year wasreported to be present in 89.1% (n=205) of the cases. Sexual assault was experienced by 1.3% (n=3) of the participantswithin the last year. Of the threephysicians who were sexually assaulted, two were exposed to such violence twice and the remaining physician once (**Figure 1**).

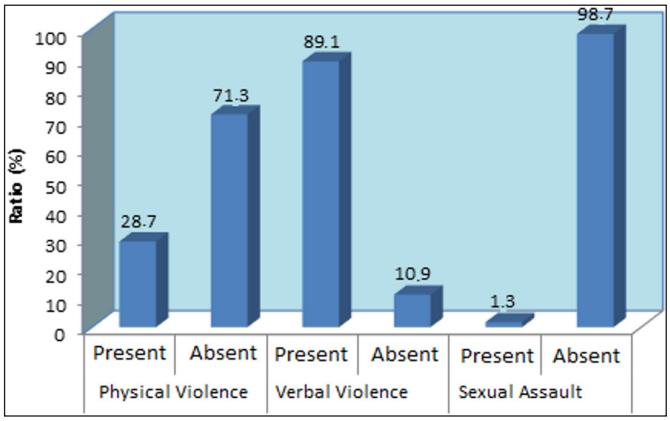

Figure 1. Distribution of violent acts according to the type of violence

The residents were exposed to violence statistically significantly more frequently than other titles (p=0.032). In the group of physicians exposed to physical violence, the number of patients admitted to the emergency department within 24 hours was significantly higher than that of other physicians (p=0.003). The number of shifts of physicians who were exposed to physical violence was significantly higher than those who were not exposed to physical violence (p=0.042). The number of shifts of physicians who were exposed to physical violence was significantly higher than those who were not exposed to physical violence (p=0.042). The number of patients that visited the emergency room in 24 hours was significantly higher for the physician group that was exposed to physical violence compared to the remaining physicians (p=0.003). The mean age of the physicians who were exposed to verbal violence was significantly lower than the mean age of thosethatwere not exposed to verbal violence (p=0.037). The rate of exposure to verbal violence was significantly higher in the female physicians than in the male physicians (p=0.045). The number of night shifts was significantly higher in the group that was exposed to verbal violence compared to the remaining physicians (p=0.008) (**Table 2**).

Lastly, a statistically significant difference was detected in the number of security personnel working per shifts in the emergency department according to the presence of verbal violence (p=0.013). The number of security personnel working in a single shift in the emergency department was significantly higher in the group that was exposed to verbal violence compared to the remaining participants.

The physicians who have experienced violence have identified the following factors, in order of frequency, as the violence's causes: low educational levels of patients' family members, patient requests for unneeded medical practices, incorrect information in the press, and patients' desire to be evaluated before their time, and the others (**Figure 2**).

Table 2. Evaluation of descriptive characteristics according to physical and verbal violence

	Physical Violence		p	Verbal Violence		p
	Yes (n=66)	No (n=164)		Yes (n=205)	No (n=25)	
Age			[a]0.642			[a]0.037*
Min-Max	25-45	24-55		25-55	24-47	
Mean±SD	32,36±5,46	32.74±5.67		32.37±5.43	34.84±6.55	
	n (%)	n (%)		n (%)	n (%)	
Gender			[b]0.068			[c]0.045*
Male	49 (%74.2)	101 (61.6%)		129 (62.9%)	21 (84%)	
Female	17 (%25.8)	63 (38.4%)		76 (37.1%)	4 (16%)	
Institution			[b]0.254			[b]0.211
State hospital	3 (%4.5)	8 (4.9%)		10 (4.9%)	1 (4%)	
Training and research hospital	44 (%66.7)	87 (53%)		121 (59%)	10 (40%)	
Medical faculty	18 (%27.3)	62 (37.8%)		68 (33.2%)	12 (48%)	
Special	1 (%1.5)	7 (4.3%)		6 (2.9%)	2 (8%)	
Title			[b]0.032*			[b]0.057
Resident	42 (%63.7)	92 (56.1%)		125 (61%)	9 (36%)	
Specialist	15 (%22.7)	62 (37.8%)		64 (31.2%)	13 (52%)	
Other	9 (%13.6)	10 (6.1%)		16 (7.8%)	3 (12%)	
Number of patients			[d]0.003**			[d]0.017*
Min-Max (Median)	70-2000 (800)	30-1800 (600)		45-2000 (700)	30-1500 (350)	
Mean±SD	765.68±394.27	616.07±408.24		680.34±406.24	484±397.79	
Work duration			[d]0.916			[d]0.130
Min-Max (Median)	1-21 (3.5)	1-31 (3.0)		1-31 (3.0)	1-20 (5.0)	
Mean±SD	5.38±5.25	5.32±5.28		5.08±5.07	7.44±6.29	
Number of night shifts			[d]0.085			[d]0.008**
Min-Max (Median)	0-12 (10)	0-15 (9)		0-15 (9)	0-14 (7)	
Mean±SD	8.59±2.73	7.73±3.75		8.23±3.28	5.88±4.56	
Number of day shifts			[d]0.194			[d]0.661
Min-Max (Median)	0-20 (10)	0-20 (10)		0-20 (10)	0-20 (10)	
Mean±SD	10.44±4.87	10.01±4.82		10.16±4.59	9.92±6.58	
Number of shifts			[d]0.042*			[d]0.193
Min-Max (Median)	0-30 (20)	0-28 (19)		0-30 (20)	0-28 (18)	
Mean±SD	19.03±5.76	17.74±5.62		18.39±5.27	15.80±8.11	

[a]Student-t Test, [b]Pearson Ki-kare Test, [c]Yates Continuity Correction Test, [d]Mann-Whitney U Test, *p<0.05, **p<0.01

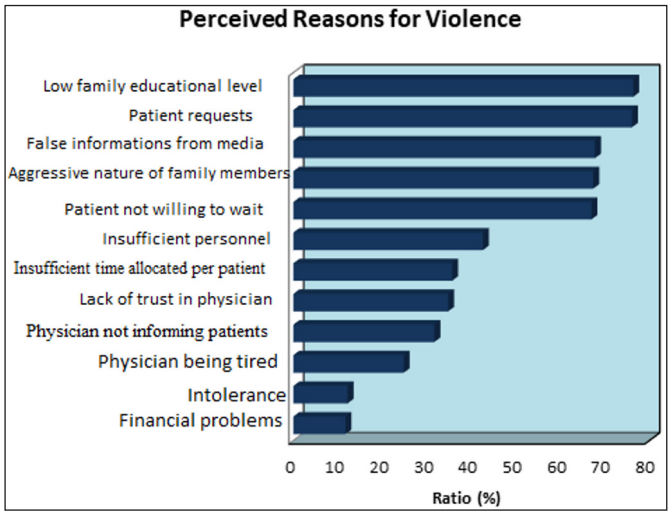

Figure 2. Distribution of participants' thoughts on the reasons for violence

DISCUSSION

In our study, when we examined the physicians' exposure to violence, we determined that verbal violence was more common than physical violence. In a study conducted by Tuğçe et al. (6), the rates of verbal, physical, and sexual violence were detectedas 60.7% (n=275), 20.5% (n=93), and 2.9% (n=13), respectively (6). Çamcı et al. (7) reported that the rate of exposure to violence was 72.4% in healthcare providers. Ayrancı et al. (8) determined that 49.5% of healthcare workers were exposed at least one type of violence.In the current study, the rate of exposure to violence was similar to the literature.

In this study, we also evaluated the physicians' perceptions of the causes of violence in the emergency department and determined that high rates of violence were due to the low educational level of the family members of patients, patient requests for unnecessary medical practices, false information published in the press, aggressive nature of family members, and patients' desire to be examined before their turn. In a study carried out by Özişli et al. (2) in the Marmara region, the causes of violence were determined as patients and their relatives being impatient, not being fully informed, and having a low educational level such our findings.

We observed a statistically significant difference between the titles of the physicians according to their exposure to physical violence. Ayrancı et al. (9) reported that nurses constituted the group that was most exposed to violence, followed by general practitioners, while faculty members were least exposed to violence. The specialists not caring for as many patients as residents may also have reduced theirrecent rate of exposure to violence.

There may be a relationship between patient density and violence. Eroglu et al. (10) reported a relationship between violence and the overcrowded nature of the emergency department. The increase in the number of patients may also increase the workload of physicians, thus reducing the quality of health services provided and leading to violence. Since studies focusing on this relationship are rare in the literature, it is obvious that it is a topic that remains up-to-date.

According to our study, as the number of shifts worked by the physicians increased, their exposure to physical violence increased. Pınar et al. (11) also showed that increased working hours and working in shifts were independent risk factors for experiencing violence. Aksakal et al. (12) determined that working more than 40 hours in a week increased the risk of physical violence by 1.86 times.

There was a significant difference in the ages of the physicians who were exposed to verbal violence compared to those without this experience. In a study by Mirza et al. (13) junior physicians were found to be more likely to report deterioration in work performance compared to their senior colleagues. İlhan et al. (14) stated that people aged less than 25 years were exposed to more violence. We consider that having experience in the profession reduces the rate of violence since it facilitates the better management of emergency services.

The rate of exposure to verbal violence was significantly higher among the female physicians compared to the male physicians. Ertanet al. (15) found that women were more exposed to verbal violence. From a social point of view, it can be stated that physical violence against men and verbal violence against women are more common.

As the number of patients treated by the physicians increased, their exposure to verbal violence increased. Ertanet al. (15) reported that the rate of exposure to violence was 31.9% among physicians that provided care for 10 or fewer patients a day, while this rate increased to 50.2% for those who saw 10-50 patients a day and 71.2% for those who saw 50 or more patients. We consider that prolonging the time allocated per patient and increasing communication with the patient can reduce the incidence of violence.

As the number of night shifts worked by the physicians increased, their exposure to verbal violence also increased.In a study by Ready (16) investigating violence against healthcare workers, an interesting finding was that working in shifts and increased working hours were risk factors for physical violence but did not appear to be risk factors in other types of violence.

CONCLUSION

The problem of violence in emergency services is multifaceted. We believe that measures should be taken by focusing on education levels, socioeconomic conditions and other factors in order to eliminate the causes of violence. Raising awareness of the public, not using emergency services unnecessarily, informing the press accurately, and paying attention to the order of examination can reduce violence in the emergency department. In addition, the improvement of the working conditions of physicians can reduce violence to which they are exposed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of University of Health Sciences, Fatih Sultan Mehmet Training and Research Hospital Clinical Researches Ethics Committee (Date: 14.04.2022, Decision No: 2022/7).

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

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

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

REFERENCES

1. Krug EG, Mercy JA, Dahlberg LL, Zwi AB. The world report on violence and health. Lancet 2002; 360: 1083-8.
2. Özişli Ö. Sağlikta şiddetin nedenleri üzerine bir araştirma. Usaysad Derg 2022; 1: 62-8.
3. Türkmenoğlu B, Sümer HE Sivas il merkezi sağlık çalışanlarında şiddete maruziyet sıklığı. Ank Med J 2017; 17: 216-25.
4. Adaş EB, Elbek O, Bakır K. Sağlık sektöründe şiddet: Hekimlere yönelik şiddet ve hekimlerin şiddet algısı. Gaziantep: Gaziantep Kilis Tabip Odası Yayını 2008.
5. Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department crowding: A systematic review of causes, consequences and solutions. PLoS One 2018; 13: e0203316.
6. Tuğçe ER, Ayoğlu F, Açikgöz B. Sağlık çalışanına yönelik şiddet: Risk faktörleri, etkileri, değerlendirilmesi ve önlenmesi. Turk J Public Health 2021; 19: 69-78.
7. Çamcı O, Kutlu Y. Kocaeli'nde sağlık çalışanlarına yönelik iş yeri şiddetinin belirlenmesi. Psikiyatr Hemşire Derg 2011; 2: 9-16.
8. Ayranci U, Yenilmez C, Balci Y, Kaptanoglu C. Identification of violence in Turkish health care settings. J Interpers Violence 2006; 21: 276-96.
9. Ayranci Ü, Yenilmez Ç, Günay Y, Kaptanoglu C. Çesitli saglik kurumlarinda ve saglik meslek gruplarinda siddete ugrama sikligi/the frequency of being exposed to violence in the various health institutions and health profession groups. Anadolu Psikiyatri Derg 2002; 3: 147.
10. Eroglu SE, Onur O, Sagiroglu E, Denizbasi A, Akoglu H. Analysis of violence in a crowded emergency room. Br J Med Med Res 2013; 3: 1208.
11. Pinar T, Acikel C, Pinar R, et al. Workplace violence in the health sector in Turkey: a national study. J Interpers Violence 2017; 32: 2345-65.
12. Aksakal FNB, Karaşahin EF, Dikmen AU, Avci E, Özkan S. Workplace physical violence, verbal violence, and mobbing experiencedby nurses at a university hospital. Turk J Med Sci 2015; 45: 1360-8
13. Mirza NM, Amjad AI, Bhatti ABH, et al. Violence and abuse faced by junior physicians in the emergency department from patients and their caretakers: a nationwide study from Pakistan. J Emerg Med 2012; 42: 727-33.
14. İlhan MN, Özkan S, Kurtcebe ZÖ, Aksakal FN. Gazi Üniversitesi Tıp Fakültesi Hastanesinde çalışan araştırma görevlileri ve intörn doktorlarda şiddete maruziyet ve şiddetle ilişkili etmenler. Toplum Hekim Bul 2009; 28: 15-23.
15. Erten R, Öztora S, Dağdeviren HN. Sağlık kuruluşlarında doktorlara yönelik şiddet maruziyetinin değerlendirilmesi. Türk Aile Hek Derg 2019; 23: 52-63.
16. Ready FN. Sağlık çalışanları şiddet araştırması. Sağlık-Sen Yayınları 2013.
17. AydemIer I, Üçlü R, Aydogan A. Acil servis personeline gore siddetin nedenleri/according to the emergency room staff the reasons for violence. J Ist Faculty Med 2020; 83: 60-9.

Original Article

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Evaluation of risk factors and outcomes associated with mortality after hip fracture surgery in eldery patients

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ABSTRACT

Objective: In this retrospective study, it was aimed to compare mortality related risk factors and outcomes in patients who underwent proximal femoral nail and partial hip prosthesis for hip fracture.

Material and Method: In our study, a total of 618 patient files who underwent hip fracture operations, including partial hip replacement (n=350) and proximal femoral nail (n=268) were retrospectively analyzed. Age, gender, fracture side, cause, type of fracture, type of operation, blood transfusion, hospital stay, anesthesia type and one-year survival times of the patients were examined.

Results: Gender, age, side, mechanism, anesthesia, comorbid diseases, cause of mortality, one-year mortality and survival time differences between patient groups were not statistically significant ($p>0.05$). However, fracture type, blood transfusion and hospital stay differences between groups were statistically significant ($p<0.05$). According to the correlation analysis results, there was a statistically significant relationship between the type of operation and the type of fracture, blood transfusion and hospital stay ($p<0.05$). The difference between level of fracture type and blood transfusion level was statistically significant ($p<0.05$). The difference in length of hospital stay was not significant at the multivariate level ($p> 0.05$). The mean survival time of the hip prosthesis group (144.97±9.83) was greater than the survival time of the proximal femoral nail group (129.72±12.31), but this difference was not statistically significant ($p> 0.05$).

Conclusion: According to the results of the research, both partial hip replacement and proximal femoral nail methods have similar results and mortality level. Therefore, methods including less invasive procedures should be preferred for the benefit of the patient in the selection of methods in hip fracture treatment.

Keywords: Hip fracture, mortality, hip replacement, risk factors

INTRODUCTION

Most hip fracture injuries occur in older people as a result of factors including falls and accidents (1-6). The proximal femaral nail (PFN) approach and partial hip replacement are two of the most popular surgical choices, despite the fact that surgical applications vary slightly based on the patient's condition, the type of injury, or other aspects of the surgical intervention (7-9).

While hip fracture is 34 per hundred thousand in men, it is 63 per hundred thousand in women. Generally, 90% of hip fractures are seen over the age of 60 (10). Although the PFN method and partial prosthesis are two common methods, there has been an increase in recent years that the PFN method involves less invasive procedures and therefore has a lower fracture risk (1). On the other hand, no study has been found that compares the two methods sufficiently. In a study conducted in 2021, which is one of the limited studies on this subject, a lower rate of fracture was observed in patients after PFN (11).

Due to the occurrence of hip fractures in older ages and health conditions that develop due to age, the management of the surgical intervention to be applied for the disease is difficult and increases the mortality of the disease. In the literature, in-hospital mortality rates after hip fracture surgery vary between %2.7 and %15, while one-year mortality rates vary between %11.5 and %58.3 (12). Although risk factors are the subject of many studies due to high mortality rates, there are not enough clinical studies comparing surgical methods. Therefore, in this study, it was aimed to compare risk factors and outcomes associated with mortality in patients treated with PFN and partial hip replacement.

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MATERIAL AND METHOD

The study was carried out with the permission of Hitit University Faculty of Medicine Clinical Research Ethics Committee (Date: 10.03.2021, Decision No: 2021/426). All procedures were carried out in accordance with the ethical rules and the principles of the declaration of Helsinki.

Study Design and Settings

Following the approval of the local ethics committee the files of 618 patients over the age of 65 who applied to our hospital with a hip fracture and were treated surgically with partial fracture side, cause of fracture, fracture type, presence of comorbid disease, operation type, blood transfusion, length of stay and anesthesia type, and one-year survival time were recorded. In the study, given hypothesis was tested: H0: There is not a statistically significant difference between proximal femoral nail and partial hip prosthesis for hip fracture.

Since fracture type is a prognostic and intercorrelated factor, its effect was evaluated in the binary logistic regression analysis as multivariate analysis metehod (12). Cemented arthroplasty was applied. Since both fracture type and surgical method differ, a multivariate analysis was performed to evaluate the effect of all of them together and the results were compared with univariate.

The primary choice for pertochanteric fractures was PFN, and subgroups of all patients were grouped according to PFN appropriate indications by stratified sampling method and multivariate analysis was performed. Inclusion and exclusion criteria were as follows:

a. No lack of information in the patient file
b. Hip fracture surgery patients
c. No presence of a medical condition or drug use that would interfere with research results
d. Having similar rehabilitation and mobilization conditions
e. Over 70 ages

Statistical Analysis

In the study, frequency analysis was used to define nominal and ordinal data, and mean and standard deviation values were used to define measurement parameters. Chi-Square and Chi-Square Similarity Ratios were used in the difference analysis of ordinal and nominal data. Before the analysis of the measurement data, Kolmogorov Smirnov Test was performed for normality distribution analysis. Nonparametric tests were used as all parameters did not conform to normal distribution as a result of the test. Mann Whitney U was used for pairwise group differences and Spearman's rho correlation analysis was used for relational analysis. Binary Logistic Regression analysis was performed for analysis at multivariate level. Kaplan Meier and Log Rank (Mantel-Cox) tests were used for the difference between cumulative survival levels. All analyzes were performed at %95 confidence interval and 0.05 significance level using SPSS 17.0 for Windows program.

RESULTS

The differences of sex, age, side, mechanism, anesthesia, comorbid diseases, cause of mortality, one-year mortality and survival time between the two groups were not statistically significant ($p>0.05$). On the other hand, the differences between the groups in terms of fracture type, blood transfusion and hospital stay were statistically significant ($p<0.05$). While femoral neck fracture was seen in the majority of the hip prosthesis group (%65.4), the majority of the PFN group had a trochanteric fracture (%56.3). Hospital stay and mean blood transfusion were higher in the hip replacement group ($p<0.05$) (**Table 1**).

According to correlation analysis results, there was a statistically significant relationship between operation type and fracture type, blood transfusion and hospital stay ($p<0.05$). These relationships are positive between fracture type and operation type; and negative between the type of operation and blood transfusion and hospital stay. In the operation type coding, 1=hip prosthesis and 2=PFN; and fracture types were coded as 1=neck fracture, 2=Trochanteric and 3=Subtrochanteric. Therefore, when the type of operation was heavily PFN, the length of stay and blood transfusion decreased. PFN was found to be the more preferred type of operation in the neck fracture in trochanteric and subtrochanteric transition (**Table 2**).

Table 2. Spearman's rho correlation analysis results between significant parameters of patient groups

	R	P
Fracture type	0.291**	0.000
Blood transfusion	-0.124**	0.002
Hospital stay	-0.095*	0.018

*p<0.05 **p<0.01

Binary logistic regression analysis results showed that the difference between the groups in multivariate level of fracture type and blood transfusion level was statistically significant ($p<0.05$). On the other hand, although the difference in length of hospital stay was significant at the univariate level, it was not significant at the multivariate level ($p>0.05$) (**Table 3**).

Table 1. Demographic and clinical characteristics of patient groups

	Hip Replacement (n=350)	PFN (n=268)	Total (n=618)	p value
Gender, n (%)				
Male	153 (43.7)	125 (46.6)	278 (45.0)	0.468[a]
Female	197 (56.3)	143 (53.4)	340 (55.0)	
Age, mean±SD	85.65±6.25	84.69±5.81	85.24±6.08	0.065[b]
Side, n (%)				
Right	175 (50.0)	134 (50.0)	309 (50.0)	>0.05[a]
Left	175 (50.0)	134 (50.0)	309 (50.0)	
Mechanism, n (%)				
Fall	307 (87.7)	229 (85.4)	536 (86.7)	0.410[a]
Traffic accident	43 (12.3)	39 (14.6)	82 (13.3)	
Fracture type, n (%)				
Femoral neck fracture	229 (65.4)	91 (34.0)	320 (51.8)	
Trochanteric	97 (27.7)	151 (56.3)	248 (40.1)	0.000[a]
Subtrochanteric	24 (6.9)	26 (9.7)	50 (8.1)	
Anesthesia, n (%)				
GA	119 (34.0)	93 (34.7)	212 (34.3)	0.856[a]
SA	231 (66.0)	175 (65.3)	406 (65.7)	
Blood transfusion, mean±SD	2.22±1.34	1.97±1.33	2.11±1.34	0.002[b]
Hospital stay, mean±SD	11.27±5.86	10.35±5.97	10.87±5.92	0.018[b]
DM, n (%)	65 (18.6)	47 (17.5)	112 (18.1)	0.741[a]
HT, n (%)	112 (32.0)	73 (27.2)	185 (29.9)	0.200[a]
CAD, n (%)	31 (8.9)	19 (7.1)	50 (8.1)	0.425[a]
CVE, n (%)	13 (3.7)	11 (4.1)	24 (3.9)	0.804[a]
CRF, n (%)				
Mortality cause, n (%)				
Cardiac arrest	4 (3.3)	5 (6.2)	9 (4.5)	
Respiratory failure	2 (1.7)	2 (2.5)	4 (2.0)	
Sepsis	1 (0.8)	1 (1.2)	2 (1.0)	0.705c
PTE	1 (0.8)	-	1 (0.5)	
Other	112 (93.3)	73 (90.1)	185 (92.0)	
One-year mortality, n (%)	120 (34.3)	81 (30.2)	201 (32.5)	0.285[a]
Survival, days, mean±SD	144.97±107.71	129.72±110.83	138.82±108.96	0.223[b]

a. Chi-Square Test, b. Mann Whitney U Test, c. Chi-Square Likelihood Ratio, GA: General Anesthesia, SA: Spinal Anesthesia, DM: Diabetes Mellitus, HT: Hypertension, CAD: Chronic artery Disease, CVE: Cerebro Vascular Event, CRF: Chronic Renal Failure, SD: Standard Deviation, PTE: PulmonerTromboemboli,

Table 3. Binary logistic regression analysis results for significant parameters of patient groups

	B	S.E.	Wald	p	OR	95% C.I.for OR	
						Lower	Upper
Fracture type			57.583	.000			
Fracture type (1)	-.999	.311	10.342	.001	.368	.200	.677
Fracture type (2)	.360	.313	1.322	.250	1.433	.776	2.649
Blood transfusion	-.153	.066	5.369	.020	.858	.754	.977
Hospital stay	-.020	.016	1.567	.211	.980	.950	1.011
Constant	.614	.356	2.970	.085	1.847		

Cox & Snell R2: 0.107; Nagelkerke R2: 0.144, [1]: Femoral neck fracture, [2]: Torocontractic fracture

Both the mean and the range of blood transfusion levels were higher in the hip replacement group. Blood transfusion needs of the patients in the PFN group were closer to each other (**Figure 1**).

Although there was a statistically significant difference between hip prosthesis and PFN group in terms of operation preference, this difference was mostly valid in hip fractures due to falls. In traffic accident-related fractures, there was no significant difference between operation preferences in cases with the same fracture type (p>0.05) (**Figure 2**).

Although the mean survival time of the hip prosthesis group (144.97±9.83) was longer than the survival time of the PFN group (129.72±12.31), the results of the Log Rank (Mantel-Cox) test showed that this difference was not statistically significant (p>0.05) (**Figure 3**).

One-year mortality was %32.5 in all patients, %34.3 in the hip prosthesis group and %30.2 in the PFN group, and the differences between the groups were not statistically significant (p>0.05) (**Figure 4**). The mean age of the patients who died in the PFN group was 85.60±6.57, while it was 87.35±6.74 in the hip replacement group.

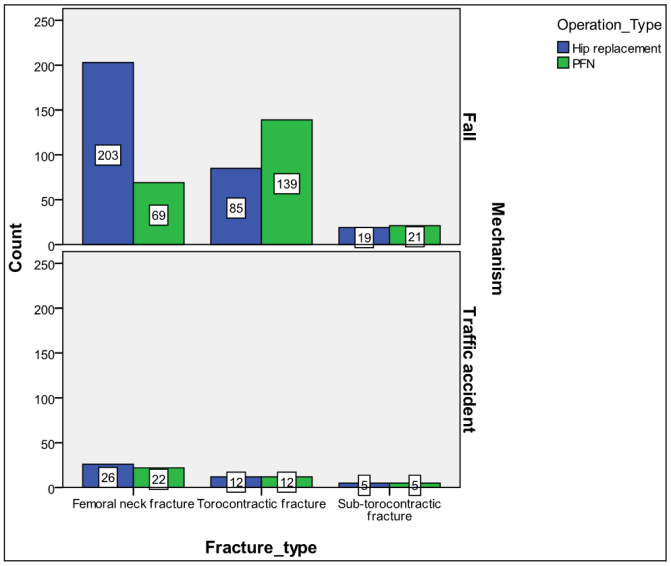

Figure 1. Distribution of blood transfusion values of patients

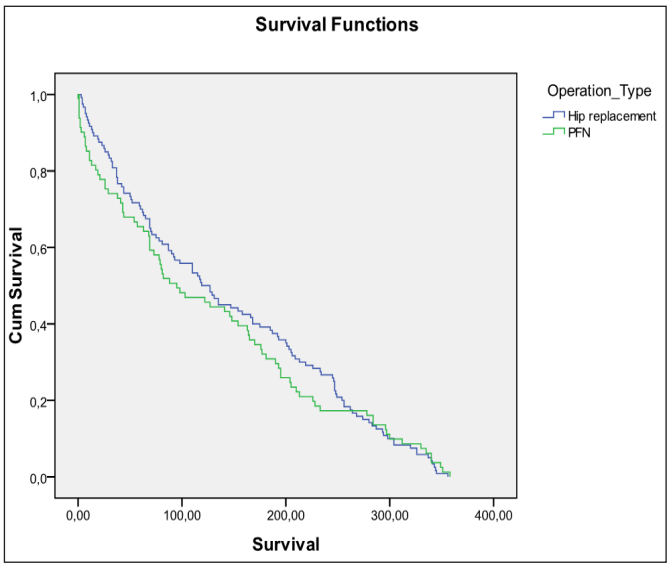

Figure 2. Distribution of fracture type and mechanism parameters of patients

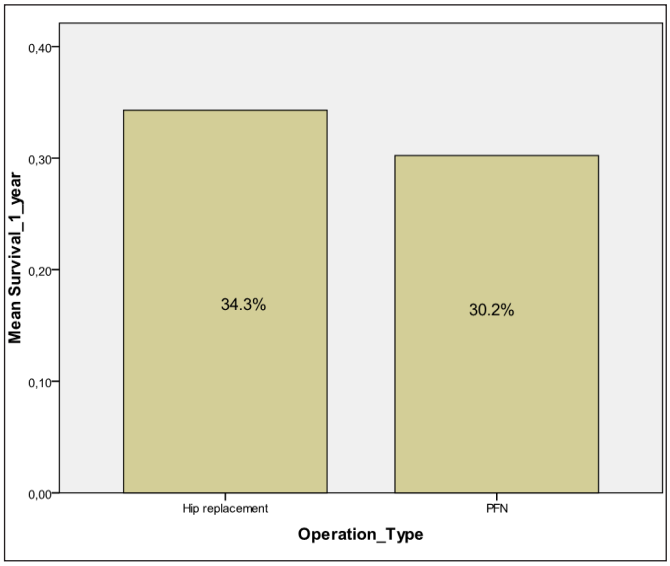

Figure 3. One-year survival and cumulative survival distribution of patients

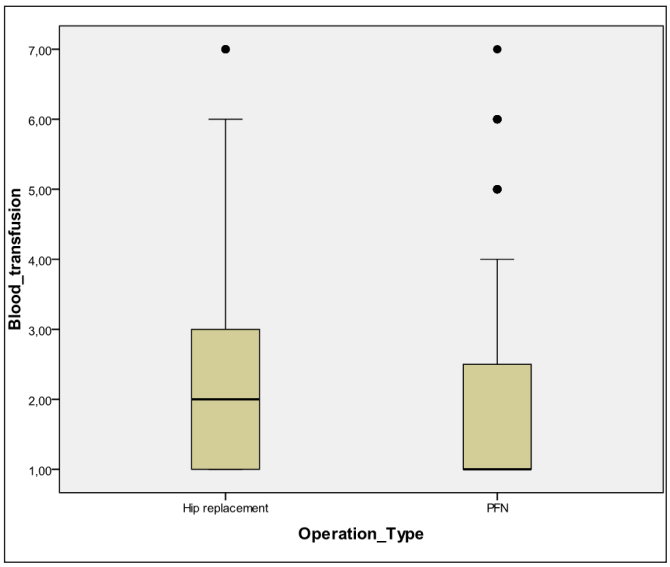

Figure 4. One-year mortality rates by operation groups

DISCUSSION

In this study, the outputs and mortality rates of hip prosthesis and PFN methods were compared in hip fracture cases, which are important guests of the orthopedic field and have high mortality rates.

Studies in the literature on hip fractures have reported that it is more common in older age and women (13-17). In our study, women were in the majority compared to men in cases treated with both methods, and %55 of all cases were women. Their average age was over 85, and the majority (%86.7) had hip fracture surgery due to a fall.

Richmond et al. (18) reported the rate of femoral neck fracture as %51.4 in their study.In our study, femoral neck fracture was found as %51.8 in total. While hip replacement was the most preferred method in this type of fracture, PFN was the most preferred surgical method in trochanteric fractures. Although the defects in the anatomical structure of the bone in femoral neck or trochanteric fractures are different, the use of both methods for each other (femoral neck fractures and trochanteric fractures) was also very high. In both methods, the use of spinal anesthesia was more common.

In our study, both blood transfusion and hospital stay were significantly higher in the hip replacement group compared to the PFN group. Thus, the PFN method seems to be a favorable method in terms of blood transfusion and hospital stay. As a matter of fact, the multivariate analysis results revealed that when all variables were considered together, there was no significant difference in the hospital stay between the two patient groups. When this finding is evaluated together, the difference between the two methods is

limited to the type of fracture and blood transfusion. The difference in blood transfusion is thought to be due to the fact that hip prosthesis application is a more major surgery than PFN.

Hypertension (HT), Diabetes Mellitus (DM), Chronic Artery Disease (CAD), and Chronic Renal Failure (CRF) are the leading comorbidities that can affect any surgical operation process. The presence of these diseases affects both the anesthesia process and the treatment process during and after the operation. Therefore, the surgical method to be applied in the presence of comorbid diseases may differ. In our study, the comorbid disease distributions of both groups were similar and the differences between the groups were not statistically significant. Therefore, it can be stated that comorbidity does not have a significant effect on the choice of surgical method in hip fractures, since the study was retrospective and it was not possible to have bias or bias in the selection of patient groups.

In the literature, different rates are given in studies on mortality after hip fracture. Pollmann et al. (6) the annual mortality as %22.8 in both groups treated as traditional method and fast track. Richmond et al. (18) in-hospital mortality as %2.7 and one-year mortality as %11.5. Leibson et al. (19) one-year mortality as %20 in patients who had hip fracture surgery, and %11 in the control group (20). Bentler et al. (21) that the one-year mortality after hip fracture was %26. Therefore, not only hip fracture mortality is included in the one-year mortality. Generally, most of clinical studies reported higher mortality in men (22-25). In another study, Wehren et al. (26) that the mortality was 31.4% in women and %23.3 in men, and %18.9 in all patients. In our study, one-year mortality was found as %32.5 in all patients, %34.3 in the hip prosthesis group and %30.2 in the PFN group, and the differences between the groups were not statistically significant. One-year mortality rate in patients treated with both methods was consistent with the literature. The mean survival time was 138.82 days in all patients, 144.97 in the hip replacement group and 129.72 in the PFN group, and the differences were not significant.

Our study showed that prosthesis application or PFN application alone did not affect mortality in patients with hip fractures. The fact that hip fracture cases generally occur in the advanced age group, therefore, the patient's anamnesis and comorbidities are not sufficiently recorded, there are difficulties in the follow-up of the data due to the fact that the cases are treated and followed up by different physicians in more than one service, and the functional status of the patients before the fracture is not known. The main limitations are that the information on what the preference is determined according to is not sufficiently included in the patient records and the study is single-centered. In addition, this issue could not be evaluated since sufficient data could not be reached for cost benefit analysis of the two methods. Similar limitations in the results obtained in the literature show that there is a need for well-planned multi-center studies that reveal cost analysis that evaluate possible risk factors including pre-fracture functional status of patients with multiple data analysis.

Correlation analysis resuts showed that hospital stay, fracture type and blood transfusion were effective on PFN or hip prosthesis. However, multivariate analysis results showed that only femoral neck fracture was a predictive factor for selection of surgical procedure. In literature, there is an accepted approach that PFN is a primary selection for subtrochanteric fractures. However, our results showed that its accepted for only femoral neck fractures. The fact that the study is conducted in a single center is the most important limitation of the study. Results may be extended to more general population with multi centered studies.

CONCLUSION

After hip fracture surgery, one-year mortality rates are significant and high, and studies should be conducted to reveal more risk factors. According to the results of the research, both hip replacement and PFN methods have similar results and mortality levels. Therefore, it is clear that in cases where both methods can be preferred in the treatment of hip fractures, it is necessary to choose a method that includes less invasive procedures for the benefit of the patient and is less costly in terms of public expenditures. For this, comprehensive studies including cost-benefit analysis are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Faculty of Medicine Clinical Research Ethics Committee (Date: 10.03.2021, Decision No: 2021/426).

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. Boutera A, Dybvik E, Hallan G, Gjertsen JE. Is there a weekend effect after hip fracture surgery? A study of 74,410 hip fractures reported to the Norwegian Hip Fracture Register. Acta Orthop 2020; 91: 63-8.
2. Zhang C, Feng J, Wang S, et al. Incidence of and trends in hip fracture among adults in urban China: A nationwide retrospective cohort study. PLoS Med 2020; 17: e1003180.
3. Bozkurt HH, Tokgöz MA, Yapar A and Atik OŞ. What is the importance of canal-to- diaphysis ratio on osteoporosis-related hip fractures? Eklem Hastalik Cerrahisi 2019; 30: 296-300.
4. Şener M, Onar V, Kazımoğlu C and Yağdı S. Parsiyel protez ile tedavi edilen yaşlı femur üst uç kırıklarında mortalite ve morbidite ilişkisi. Eklem Hastalıkları ve Cerrahisi 2009; 20: 11-7.
5. Kristoffersen MH, Dybvik E, Steihaug OM, et al. Validation of orthopaedic surgeons' assessment of cognitive function in patients with acute hip fracture. BMC Musculoskelet Disord 2019; 20: 268.
6. Pollmann CT, Rotterud JH, Gjertsen JE, Dahl FA, Lenvik O, Aroen A. Fast track hip fracture care and mortality - an observational study of 2230 patients. BMC Musculoskelet Disord 2019; 20: 248.
7. Alm CE, Frihagen F, Dybvik E, Matre K, Madsen JE, Gjertsen JE. Implants for trochanteric fractures in Norway: the role of the trochanteric stabilizing plate-a study on 20,902 fractures from the Norwegian hip fracture register 2011-2017. J Orthop Surg Res 2021; 16: 26.
8. Kjaervik C, Stensland E, Byhring HS, Gjertsen JE, Dybvik E, Soreide O. Hip fracture treatment in Norway: deviation from evidence-based treatment guidelines: data from the Norwegian Hip Fracture Register, 2014 to 2018. Bone Jt Open 2020; 1: 644-53.
9. Majoor BCJ, Leithner A, Van de Sande MAJ, Appelman-Dijkstra NM, Hamdy NAT, Dijkstra PDS. Individualized approach to the surgical management of fibrous dysplasia of the proximal femur. Orphanet J Rare Dis 2018; 13: 72.
10. Cauley JA, Cawthon PM, Peters KE, et al. Risk factors for hip fracture in older men: the Osteoporotic Fractures in Men Study (MrOS). J Bone Miner Res 2016; 31: 1810-9.
11. Zhang YW, Lu PP, Li YJ, et al. Prevalence, characteristics, and associated risk factors of the elderly with hip fractures: a cross-sectional analysis of NHANES 2005-2010. Clin Interv Aging 2021; 16: 177-85.
12. Schnell S, Friedman SM, Mendelson DA, Bingham KW, Kates SL. The 1-year mortality of patients treated in a hip fracture program for elders. Geriatr Orthop Surg Rehabil 2010; 1: 6-14.
13. Yang Y, Komisar V, Shishov N, et al. The effect of fall biomechanics on risk for hip fracture in older adults: a cohort study of video-captured falls in long-term care. J Bone Miner Res 2020; 35: 1914-22.
14. Barnea R, Weiss Y, Abadi-Korek I, Shemer J. The epidemiology and economic burden of hip fractures in Israel. Isr J Health Policy Res 2018; 7: 38.
15. Dyer SM, Crotty M, Fairhall N, et al. A critical review of the long-term disability outcomes following hip fracture. BMC Geriatr 2016; 16: 158.
16. Lee SH, Chen IJ, Li YH, Fan Chiang CY, Chang CH, Hsieh PH. Incidence of second hip fractures and associated mortality in Taiwan: A nationwide population-based study of 95,484 patients during 2006-2010. Acta Orthop Traumatol Turc 2016; 50: 437-42.
17. Von Friesendorff M, Besjakov J, Akesson K. Long-term survival and fracture risk after hip fracture: a 22-year follow-up in women. J Bone Miner Res 2008; 23: 1832-41.
18. Richmond J, Aharonoff GB, Zuckerman JD, Koval KJ. Mortality risk after hip fracture. J Orthop Trauma 2003; 1: 53-6.
19. Leibson CL, Tosteson AN, Gabriel SE, Ransom JE, Melton LJ. Mortality, disability, and nursing home use for persons with and without hip fracture: a population-based study. J Am Geriatr Soc 2002; 50: 1644-50.
20. Lu Y, Uppal HS. Hip fractures: relevant anatomy, classification, and biomechanics of fracture and fixation. Geriatr Orthop Surg Rehabil 2019; 10: 1-10.
21. Bentler SE, Liu L, Obrizan M, et al. The aftermath of hip fracture: discharge placement, functional status change, and mortality. Am J Epidemiol 2009; 170: 1290-9.
22. Rapp K, Büchele G, Dreinhöfer K, Bücking B, Becker C, Benzinger P. Epidemiology of hip fractures:Systematic literature review of German data and an overview of the international literature. Epidemiologie von Hüftfrakturen: Systematisches Literaturreview deutscher Daten und ein Überblick über die internationale Literatur. Z Gerontol Geriatr 2019; 52: 10-6.
23. Rapp K, Becker C, Lamb SE, Icks A, Klenk J. Hip fractures in institutionalized elderly people: incidence rates and excess mortality. J Bone Miner Res 2008; 23: 1825-31.
24. Elliott J, Beringer T, Kee F, Marsh D, Willis C, Stevenson M. Predicting survival after treatment for fracture of the proximal femur and the effect of delays to surgery. J Clin Epidemiol 2003; 56: 788-95.
25. Berry SD, Samelson EJ, Bordes M, Broe K, Kiel DP. Survival of aged nursing home residents With hip fracture.J Gerontol ABiol Sci Med Sci 2009; 64: 771-7.
26. Wehren LE, Hawkes WG, Orwig DL, Hebel JR, Zimmerman SI, Magaziner J. Gender differences in mortality after hip fracture: the role of infection. J Bone Miner Res 2003; 18: 2231-7.

Original Article

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The relationship between vitamin D deficiency and hypertensive organ damage

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ABSTRACT

Aim: In this study, we aimed to examine the relationship between vitamin D level and target organ damage (TOD) in primary hypertension patients by eliminating the effects of hypertension duration and antihypertensive treatments.

Material and Method: The study included 144 patients with primary hypertension. Vitamin D levels were classified as sufficiency (VDS), deficiency (VDD), and severe deficiency (VDSD). In case of more than one TOD indicator (microalbuminuria or proteinuria, left ventricular mass index and carotid intima-media thickness), it was considered as multi organ involvement (OI). In the multiple regression model, besides the traditional risk factors, the effects of hypertension duration and anti-hypertensive treatments were adjusted.

Results: The rates of VDS and VDD were lower in TOD (+) compared to TOD (-) (14.1% vs 51.5%, 32.1% vs 42.4%; p<0.001), while VDSD ratio was higher (53.8% vs 6.1%, p<0.001). VDSD ratio was higher in hypertensive patients with single-OI compared to TOD (-), while its was higher in patients with multi-OI compared to single-IO. In the multivariable regression model; showed that 1 ng/mL decrease in the Vitamin D increased the probability of TOD by 1.22 folds [vs TOD (-)], probability of single organ involvement by 1.19 folds [vs TOD (-)], and probability of multi-IO by 1.11 folds (vs single-IO).

Conclusion: In hypertensive patients, a decrease in vitamin D levels is associated with an increase in TOD indicators. The risk of developing TOD and multi-IO is higher in vitamin D deficiency. Vitamin D supplements may be beneficial in hypertensive organ damage, regardless of disease duration and anti-hypertensive treatments.

Keywords: Atherosclerosis, hypertension, vitamin D, target organ damage

INTRODUCTION

Vitamin D deficiency and hypertension, which are globally common public health problems, are important risk factors for cardiovascular events (1). It has been suggested that a decrease in Vitamin D levels increases blood pressure (BP) levels and may be a new risk factor in causing hypertension. (2, 3). Atherosclerosis due to cardiac and vascular tissue damage caused by high BP causes target organ damage (TOD) (4). Therefore, Vitamin D has been suggested as an important mechanism in hypertensive organ damage (5).

Organs and tissues containing vitamin D receptors, such as the heart, kidneys, and vascular endothelium, can affect renin-angiotensin system (RAAS) activation (6). This may cause endothelial or renal dysfunctions in hypertensive patients (7).The incidence of endothelial dysfunction and cardiac hypertrophy was higher in hypertensive patients with VDD (8). Previous studies have shown an inverse correlation between the Vitamin D levels and subclinical TOD indicators (carotid intima-media thickness (CIMT), left ventricular mass index (LVMI) and microalbuminuria) in hypertensive patients (9, 10). In an experimental study in rats, vitamin D depletion was shown to increase creatinine levels and affect RAAS components that may directly contribute to hypertensive organ damage (5). On the other hand, there was a positive correlation between duration of hypertension and incidence of VDD (11). However, it is unknown whether VDD in hypertension is a cause of disease or an epiphenomenon.

We hypothesized that there might be a negative correlation between duration of hypertension and multi-organ involvement and Vitamin D levels. In this study, we aimed to examine the relationship between vitamin D level and hypertensive organ damage in primary hypertension patients by eliminating the effects of hypertension duration and antihypertensive treatments.

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MATERIAL AND METHOD

This retrospective study was carried out with the permission of Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 29.06.2022, Decision No: 2022.06.21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

In this study, 618 patients who were followed up with the diagnosis of hypertension in the Cardiology Clinic from January 2021 to January 2022 were evaluated. The inclusion criteria of the study were patients aged 18 years to 65 years, with documented levels of vitamin D, microalbuminuria or proteinuria, LVMI and CIMT. The exclusion criteria were secondary hypertension, history of diabetes mellitus, asthma, chronic obstructive lung disease, rheumatic diseases, coronary artery disease, malignancy, active or chronic infections, acute or chronic kidney disease, peripheral artery disease, cerebrovascular disease, liver diseases, heart failure, presence of proteinuria at nephrotic level, patients without documented vitamin D levels, and patients without documented levels of TOD markers (microalbuminuria or proteinuria, LVMI and CIMT). Previous studies have reported a higher incidence of vitamin D deficiency in geriatric patients (aged 65 years and older) and hypertension duration of 8 years or more (11, 12). In order to avoid the bias of vitamin D deficiency, we also excluded patients in this group. A total of 474 patients with exclusion criteria were excluded from the study. Finally, 144 patients were included in the analysis.

Study Protocol

The diagnosis of hypertension was evaluated according to the 2018 ESC criteria (13), and its was defined as systolic BP (SBP) of ≥140 mmHg and diastolic BP (DBP) of ≥90 mmHg.

Microalbuminuria of >30 mg/day or proteinuria of >150 mg/day, LVMI of >95 g/m2 in women and >115 g/m2 in men, and CIMT of >0.9 mm or presence of plaque in the carotid were as the presence of TOD (14). According to these findings, the patients were divided into 2 groups as those with and without TOD and patients with more than single of the TOD indicators were evaluated as subclinical multi-organ involvement. In addition, patients were divided into 3 groups according to their vitamin D levels as follows: sufficiency ≥20 ng/mL (VDS), deficiency 10-19 ng/mL (VDD), and severe deficiency <10 ng/mL (VDSD) (15).

Demographic and laboratory data were obtained by accessing patient files through the hospital's electronic information system.

Laboratory Testing

Erythrocytes and thrombocytes were performed by impedance method, leukocytes were performed by optical laser scattering (light scattering), and other complete blood count parameters were measured with a Sysmex XE 2100 hematology analyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Microalbuminuria and proteinuria in 24 hours (by turbidimetric methods) and lipid parameters (by enzymatic colorimetric methods) were performed with a Hitachi Modular P800 autoanalyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Hemoglobin was measured photometrically. Inflammatory indices were obtained from the complete blood count as follows: neutrophil to lymphocyte ratio (NLR) = neutrophil count / lymphocyte count, platelet to lymphocyte ratio (PLR) = platelet count / lymphocyte count.

The 25-hydroxyvitamin D, which the major circulating form of vitamin D, levels were measured by radioimmunassay method (Beckman Coulter, Indianapolis, USA) in an autoanalyzer.

Echocardiographic Examination

Echocardiographic measurements were made with an echocardiography device (2.5 MHz transducer, Vivid 7, GE-Vingmed Ultrasound AS, Horten, Norway) by a blinded cardiologist. Left ventricular mass (LVM) was calculated using the Devereux formula (LVM = 1.04 × [(IVST + PWT + LVDd)3 – (LVDd)3] – 13.6) and was indexed to body surface area (16). LVMI of >95 g/m2 in women and >115 g/m2 in men were considered left ventricular hypertrophy

Carotid Ultrasonography

CIMT measurements, with the patient in the supine position and both hands under the head, were measured with a high-resolution B-mode device (Logiq 7, GE Med Inc., Chicago, IL, USA) by a radiologist blinded to the study. An automated linear probe was used for measurements from the right and left common carotid arteries. Measurements were performed at 3 points: the right carotid artery branches from the brachiocephalic trunk, the left carotid arteries from the aorta at 2 cm away, and the bifurcation of the internal carotid arteries. Longitudinal measurements were performed from distances of media-adventitia echogenicity and vessel lumen echogenicity. CIMT was calculated by taking the average of 3 measurements made for each carotid artery.

The presence of plaque was defined according to the Mannheim consensus (17). The criteria were defined as follows: a focal protrusion in the lumen measuring at least cIMT >1.5 mm; a protrusion at least 50% greater than the surrounding cIMT; or an arterial lumen encroaching >0.5 mm.

Statistical Analysis

SPSS 20 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. To determine whether or not data were normally distributed, Kolmogorov-Smirnov testing was applied. While numerical variables are given as mean ± standard deviation or median (min-max), and categorical values are given as numbers and percentages. Chi-square and Fisher's exact testing was applied to compare categorical data. Student T test or Mann-Whitney U test was used in the comparison of numerical variables in two groups according to normality distribution. ANOVA test (post hoc: Bonferroni test) or Kruskall Wallis H test (post hoc: Dunn's test) was used to compare numerical variables between Vitamin D groups and hypertensive organ involment groups according to normality distribution. Spearman correlation analysis was used for the relationship between Vitamin D and other numerical parameters. Independent predictors of TOD were determined by logistic regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 54.7±10.8 years and the mostly of them were female (63.9%). Vitamin D was sufficient in 31.3% of hypertensive patients, while it was deficient in 36.8% and severely deficient in 31.9%. Mean SBP levels, mean DBP levels, mean NLR levels were higher in VDSD group compared to the other groups. The levels of TOD indicators were higher in VDSD group compared other groups, while its were higher in VDD group compared to the VDS group (**Table 1**). The relationship between vitamin D levels and BP levels and TOD indicators is shown in **Figure 1**. A negative correlation was found between vitamin D levels and CRP levels (r= -0.305; p=0.018) and neutrophil levels (r= -0.335; p=0.005) and NLR levels (r= -0.340; p=0.004).

Table 1. Demographic and laboratory findings according to Vitamin D status in hypertension patients

Variables	All population n=144	Vitamin D			p
		Sufficiency n=45	Deficiency n=53	Severe deficiency n=46	
Demographic findings					
Age, years	53.7±10.8	54.1±9.8	53.7±11.9	53.2±10.4	0.449
Female gender, n (%)	92(63.9)	27(60.0)	31(58.5)	34(73.9)	0.230
BMI, kg/m2	30.4±5.1	29.8±4.8	29.9±5.3	31.7±5	0.118
Smoking, n (%)					0.670
Non-smoker	96(66.7)	33(73.3)	34(64.2)	29(63.0)	
Smoker	30(20.8)	6(13.3)	13(24.5)	11(23.9)	
Ex-smoker	18(12.5)	6(13.3)	6(11.3)	6(13.0)	
Alcohol use, n (%)	33(22.9)	10(22.2)	10(18.9)	13(28.3)	0.510
DoH, years	3(2-5)	2(2-5)	3(2-5)	4(2-6)	0.384
Drugs, n (%)					
ACEI/ARBs	74(51.4)	24(53.3)	29(54.7)	21(45.7)	0.646
Beta blocker	22(15.3)	6(13.3)	8(15.1)	8(17.4)	0.918
CCB	64(44.4)	20(44.4)	20(37.7)	24(52.2)	0.372
Diuretics	45(31.5)	17(38.6)	16(30.2)	12(26.1)	0.441
SBP, mm Hg	136.7±22.4	128.0±19.5	133.0±21.5	149.4±20.7	<0.001*
DBP, mm Hg	84.3±13.9	80.0±12.4	80.2±12.7	93.0±12.7	<0.001*
Laboratory findings					
Microalbuminuria, g/24h	11.4(5.4-20.8)	7.1(4.5-14)	9.2(4.8-19)	18.3(12.2-32.7)	<0.001*
Proteinuria, g/24h	92(67.9-144.1)	73.3(54-93.3)	100.4(70.2-135.6)	132.6(84-176)	<0.001*
LVMI, g/m2	93.4±17.6	84.8±17.2	93.2±15.4	104.4±17.7	<0.001*
CIMT, mm	0.9±0.2	0.8±0.1	0.9±0.2	1.0±0.2	<0.001*
WBC, x109/L	7.5±2.3	7.4±1.5	7.4±2.2	7.6±2.5	0.847
Neutrophil, x109/L	4.7±1.4	4.4±1.2	4.4±1.4	5.3±1.5	0.002*
Platelet, x109/L	304.4±63.7	301.2±57.4	309.8±67.7	301.3±65.8	0.741
Lymphocyte, x109/L	2.2±0.7	2.2±0.6	2.3±0.9	2.2±0.6	0.723
NLR	2.3±0.7	2.1±0.7	2.1±0.8	2.5±0.7	0.008*
PLR	146.5±38.2	143.7±35.5	149.2±43.9	146.2±36.5	0.822
FBG, mg/dL	96.8±14.4	96.6±11.5	94.1±11.8	100.1±18.6	0.123
Hemoglobin, g/dL	13.9±1.5	13.9±1.4	13.9±1.4	13.9±1.6	0.964
Total cholestrol, mg/dL	202.5±42.5	200.5±46.2	211.7±32.4	194.1±47.3	0.120
LDL, mg/dL	121.5±36.4	118.9±38	130.2±29.4	114.2±40.7	0.084
HDL, mg/dL	50.5±13.3	51.4±12.3	50.6±13.7	49.3±14	0.748
Triglyceride, mg/dL	136(97-196)	136(100-196)	138(94-196)	125(97-200)	0.903
Albumin, g/dL	4.6±0.4	4.6±0.3	4.6±0.4	4.5±0.3	0.418
CRP, mg/dL	3.5(2-6.3)	2.7(2-5.1)	4(2.1-6.6)	3.8(1.8-7.6)	0.560
Vitamin D, ng/mL	15.1(9.6-21.6)	24.9(22.2-28.1)	15.2(12.9-18.3)	7.2(5.6-9.3)	<0.001*

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as number (%). * p < 0.05 shows statistical significance. Bold characters differ between groups (post-hoc: Bonferroni or Dunn's test) Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers, CIMT, carotid intima media thickness; CRP, C – reactive protein; DBP, diastolic blood pressure; DoH, duration of hypertension; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; LVMI, left ventricular mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; WBC, white blood count.

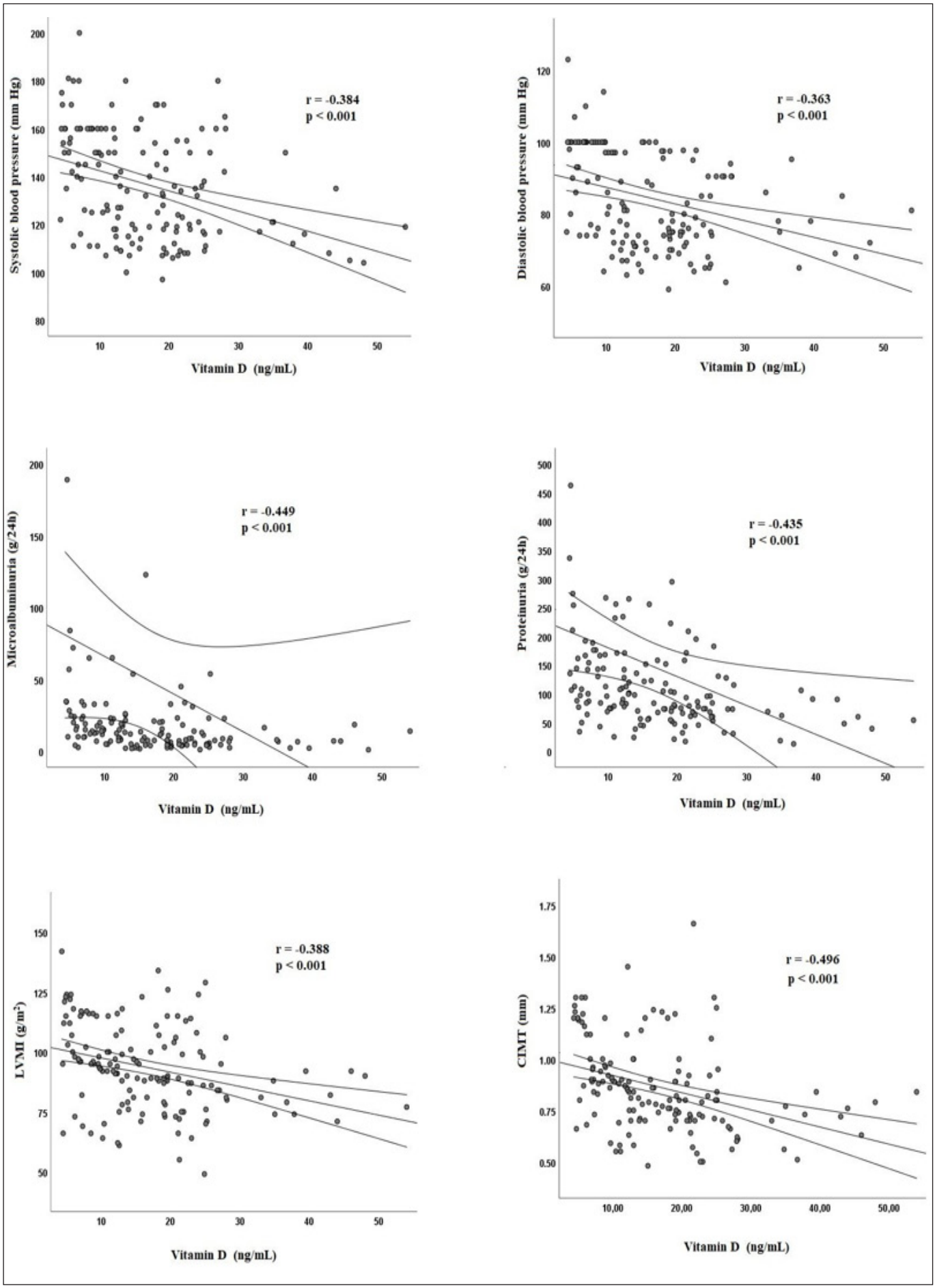

Figure 1. Scatter plot representation of the negative correlation between levels of vitamin D, blood pressure and TOD indicators

Mean NLR, mean PLR, and median CRP levels were higher in TOD (+) compared to TOD (-), while median Vitamin D level was lower (10 vs 20.7 ng/mL, p<0.001) (**Table 2**). Mean NLR, mean PLR, and median CRP levels were higher in hypertensive patients with single-organ involvement compared to TOD (-), while median Vitamin D level was lower (**Table 3**). In addition, mean NLR and median CRP levels were higher in hypertensive patients with mutli-organ involvement compared to single-organ involvement, while median Vitamin D levels were lower (**Table 3**).

Table 2. Demographic and laboratory findings according to presence of target organ damage in hypertension patients

Variables	Target Organ Damage		p
	No n=66	Yes n=78	
Demographic findings			
Age, years	55.2±10.7	54.3±10.9	0.563
Female gender, n (%)	39 (59.1)	53 (67.9)	0.299
BMI, kg/m2	29.6±5.2	31.1±5.0	0.077
Smoking, n (%)			0.815
Non-smoker	42 (63.6)	54 (69.2)	
Smoker	15 (22.7)	15 (19.2)	
Ex-smoker	9 (13.6)	9 (11.5)	
Alcohol use, n (%)	13 (19.7)	20 (25.6)	0.432
DoH, years	2 (2-5)	3.5 (2-6)	0.180
Drugs, n (%)			
ACEI/ARBs	39 (59.1)	35 (44.9)	0.089
Beta blocker	9 (13.6)	13 (16.7)	0.650
CCB	25 (37.9)	39 (50.0)	0.179
Diuretics	22 (33.8)	23 (29.5)	0.592
SBP, mm Hg	133.4±22.4	139.5±22.1	0.104
DBP, mm Hg	82.5±13.4	85.7±14.2	0.168
Laboratory findings			
Microalbuminuria, g/24h	6.8 (4.4-9)	19.5 (10.9-32.7)	<0.001*
Proteinuria, g/24h	69.8 (52-90.8)	138.8 (84-188.7)	<0.001*
LVMI, g/m2	84.2±11.9	101.2±18	<0.001*
CIMT, mm	0.7±0.1	1.0±0.2	<0.001*
WBC, x109/L	7.0±1.7	7.9±2.7	0.015*
Neutrophil, x109/L	4.0±0.9	5.3±1.5	<0.001*
Platelet, x109/L	284.1±54.6	321.6±66.1	<0.001*
Lymphocyte, x109/L	2.3±0.8	2.2±0.7	0.547
NLR	1.9±0.4	2.6±0.7	<0.001*
PLR	133.8±33.1	157.3±42.8	<0.001*
FBG, mg/dL	96.5±13.9	97±14.8	0.843
Hemoglobin, g/dL	14±1.4	13.8±1.6	0.320
Total cholestrol, mg/dL	199.2±37.4	205.4±46.6	0.385
LDL, mg/dL	119±32.2	123.7±39.9	0.450
HDL, mg/dL	49.3±13.6	51.5±13	0.347
Triglyceride, mg/dL	138 (97-188)	129 (96-201)	0.885
Albumin, g/dL	4.6±0.4	4.5±0.3	0.475
CRP, mg/dL	2.6 (1.6-5.4)	4.5 (2.6-6.9)	0.009*
Vitamin D, ng/mL	20.7 (14.6-26.7)	10 (7-17.9)	<0.001*
Sufficiency, n (%)	34 (51.5)	11 (14.1)	<0.001*
Deficiency, n (%)	28 (42.4)	25 (32.1)	<0.001*
Severe deficiency, n (%)	4 (6.1)	42 (53.8)	<0.001*

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as number (%). * p < 0.05 shows statistical significance. Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers, CIMT, carotid intima media thickness; CRP, C – reactive protein; DBP, diastolic blood pressure; DoH, duration of hypertension; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; LVMI, left ventricular mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; WBC, white blood count.

The rates of VDS and VDD were lower in TOD (+) compared to TOD (-) (14.1% vs 51.5%, 32.1% vs 42.4%; p<0.001), while VDSD ratio was higher (53.8% vs 6.1%, p<0.001) (**Table 2**). VDSD ratio was higher in hypertensive patients with single organ involvement compared to TOD (-), while its was higher in patients with multi-organ involvement compared to single-organ involvement (**Figure 2**) (**Table 3**).

In the multivariable regression model, increased NLR levels and decreased Vitamin D were determined as common independent predictors of the presence of TOD and single organ involvement. Independent predictors of multi-organ involvement were found to be increased SBP, increased NLR levels and decreased Vitamin D levels. According to this; it was determined that 1 ng/mL decrease in the Vitamin D increased the probability of TOD by 1.22 folds [TOD (-)], probability of single organ involvement by 1.19 folds [vs TOD (-)], and probability of multi-organ involvement by 1.11 folds (vs single organ involvement) (**Table 4**).

Table 4. Independent predictors for presence of target organ damage and multi-organ involvement

Variables	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
TOD (+) (ref: TOD(-))						
WBC	1.22	1.03-1.44	0.019*	-	-	-
Neutrophil	2.44	1.69-3.54	<0.001*	-	-	-
Platelet	1.02	1.01-1.03	0.001*	-	-	-
NLR	8.61	3.67-20.21	<0.001*	10.22	3.51-29.82	<0.001*
PLR	1.02	1.01-1.03	<0.001*	-	-	-
CRP	1.03	1.01-1.07	0.012*	-	-	-
Vitamin D	0.84	0.78-0.89	<0.001*	0.81	0.74-0.88	<0.001*
Nagelkerke R2= 0.628, p< 0.001						
Single OI (ref: TOD(-))						
WBC	1.24	1.02-1.58	0.047*	-	-	-
Neutrophil	2.14	1.37-3.34	0.001*	-	-	-
Platelet	1.03	1.01-1.07	0.018*	-	-	-
NLR	8.06	2.77-23.45	<0.001*	9.41	2.66-33.25	<0.001*
PLR	1.02	1.01-1.03	0.027*	-	-	-
CRP	1.02	1.01-1.04	0.036*	-	-	-
Vitamin D	0.85	0.78-0.93	<0.001*	0.84	0.76-0.92	<0.001*
Nagelkerke R2= 0.497, p< 0.001						
Multi OI (ref: One OI)						
SBP	1.04	1.01-1.06	0.003*	1.03	1.01-1.06	0.009*
DBP	1.05	1.02-1.09	0.005*	-	-	-
Neutrophil	1.44	1.03-2.02	0.032*	-	-	-
NLR	2.25	1.17-4.35	0.003*	1.98	1.08-4.01	0.041*
CRP	1.04	1.01-1.08	0.046*	-	-	-
Vitamin D	0.92	0.85-0.99	0.030*	0.90	0.86-0.95	0.033*
Nagelkerke R2= 0.412, p< 0.001						

In the multivariable regression analysis, the effects of age, gender, duration of hypertension, and drug use were adjusted. * p < 0.05 shows statistical significance. Abbreviations: CI: confidence interval; CRP, C – reactive protein; DBP, diastolic blood pressure; NLR, neutrophil to lymphocyte ratio; OR: odds ratio; OI: organ involvement; PLR, platelet to lymphocyte ratio; SBP, systolic blood pressure; WBC, white blood count.

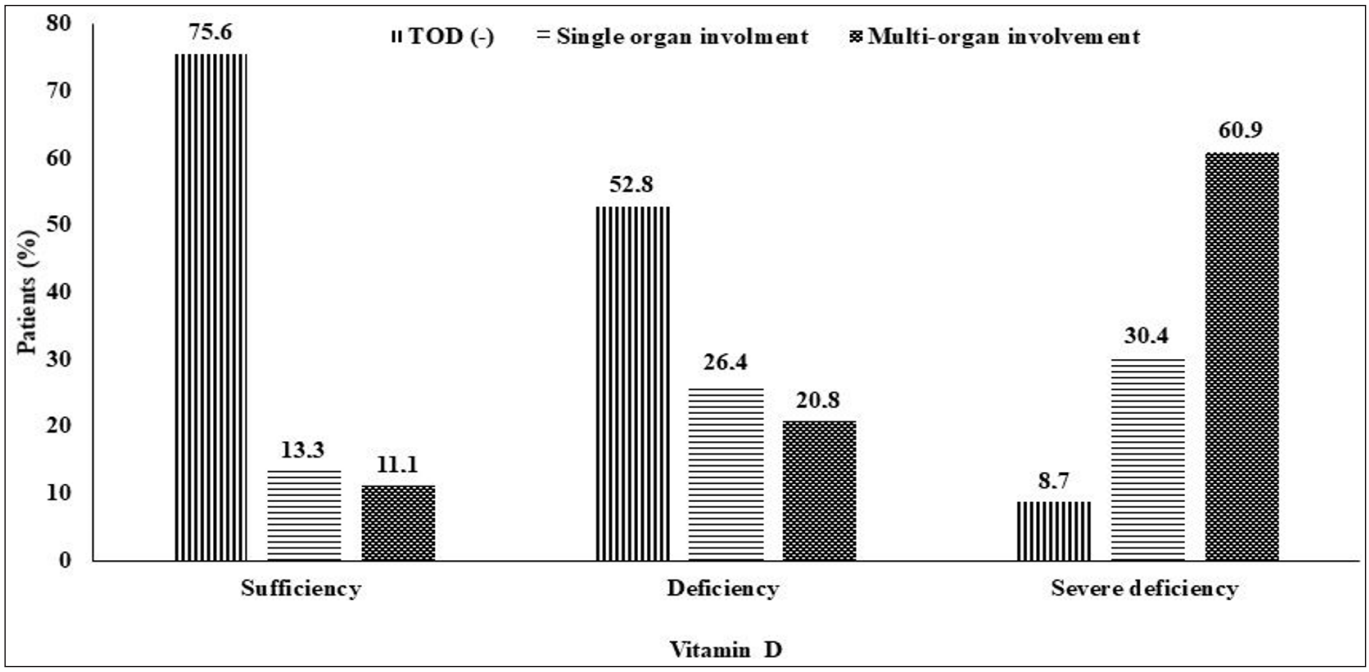

Figure 2. Distribution of hypertensive organ involvement according to vitamin D deficiency

Table 3. Demographic and laboratory findings according to organ involvement in hypertension patients

Variables	Target Organ Damage (-) n=66	Target Organ Damage (+)		p
		Single IO n=34	Multi IO n=44	
Demographic findings				
Age, years	55.2±10.7	54.7±9.8	54.0±11.6	0.465
Female gender, n (%)	39 (59.1)	22 (64.7)	31 (70.5)	0.487
BMI, kg/m2	29.6±5.2	30.8±3.7	31.4±5.8	0.179
Smoking, n (%)				0.971
Non-smoker	42 (63.6)	23 (67.6)	31 (70.5)	
Smoker	15 (22.7)	7 (20.6)	8 (18.2)	
Ex-smoker	9 (13.6)	4 (11.8)	5 (11.4)	
Alcohol use, n (%)	13 (19.7)	8 (23.5)	12 (27.3)	0.625
DoH, years	2 (2-5)	2.5 (2-6)	4 (2-6)	0.199
Drugs, n(%)				
ACEI/ARBs	39 (59.1)	13 (38.2)	22 (50.0)	0.149
Beta blocker	9 (13.6)	5 (14.7)	8 (18.2)	0.805
CCB	25 (37.9)	18 (52.9)	21 (47.7)	0.327
Diuretics	22 (33.8)	11 (32.4)	12 (27.3)	0.803
SBP, mm Hg	133.4±22.4	130.6±20.8	146.3±20.8	0.002*
DBP, mm Hg	82.5±13.4	80.4±13.3	89.8±13.7	0.004*
Laboratory findings				
Microalbuminuria, g/24h	6.8 (4.4-9)	14.8 (8-24.8)	20.8 (13-34.5)	<0.001*
Proteinuria, g/24h	69.8 (52-90.8)	103 (75.1-171)	158.1 (101.2-201.3)	<0.001*
LVMI, g/m2	84.2±11.9	94.4±19.3	106.5±15.1	<0.001*
CIMT, mm	0.7±0.1	0.9±0.2	1.1±0.2	<0.001*
WBC, x109/L	7.0±1.7	7.8±1.9	8.0±3.2	0.029*
Neutrophil, x109/L	4.0±0.9	4.8±1.1	5.8±1.6	<0.001*
Platelet, x109/L	284.1±54.6	315.6±68.2	326.2±64.8	0.001*
Lymphocyte, x109/L	2.3±0.8	2.2±0.7	2.2±0.7	0.831
FBG, mg/dL	96.5±13.9	95.9±10.6	97.9±17.6	0.810
Hemoglobin, g/dL	14.0±1.4	13.8±1.6	13.7±1.5	0.589
Total cholestrol, mg/dL	199.2±37.4	203.4±56.2	207.2±37.4	0.637
LDL, mg/dL	119.0±32.2	118.4±46.7	128.0±33.1	0.394
HDL, mg/dL	49.3±13.6	49.6±12.8	53.0±13.2	0.350
Triglyceride, mg/dL	138 (97-188)	137.5 (107-218)	121 (94-158)	0.318
Albumin, g/dL	4.6±0.4	4.6±0.2	4.5±0.4	0.301
CRP, mg/dL	2.6 (1.6-5.4)	4.0 (1.8-6.4)	5.3 (2.1-8.0)	0.028*
Vitamin D, ng/mL	20.7 (14.6-26.7)	12.6 (8.8-19.2)	8.5 (5.9-14.8)	<0.001*
Sufficiency, n (%)	34 (51.5)	6 (17.6)	5 (11.4)	<0.001*
Deficiency, n (%)	28 (42.4)	14 (41.2)	11 (25.0)	<0.001*
Severe deficiency, n (%)	4 (6.1)	14 (41.2)	28 (63.6)	<0.001*

DISCUSSION

In this study, a negative correlation was found between levels of TOD indicators and Vitamin D in hypertensive patients. The levels of TOD indicators increased gradually from VDD to VDSD, while the risk of multi-organ involvement was higher in patients with VDSD. In addition, a decreased Vitamin D level was found to be an independent predictor of both presence of TOD and multi-organ involvement. This association was independent of disease duration and anti-hypertensive treatment. These findings indicate that the risk of TOD may be higher in hypertensive patients with VDD or VDSD.

We found a negative correlation between blood pressure and Vitamin D levels in hypertensive patients. Vitamin D has a cardiovascular protective effect by taking part in the modulation of inflammatory cytokines and RAAS (18). This role of vitamin D can affect BP levels and cause an inverse relationship. In previous studies, it has been shown that a 1 ng/mL decrease in Vitamin D levels causes an increase of 0.76 mm Hg in BP (3), and increases the risk of developing hypertension by 8.1% (19). On the other hand, decreased Vitamin D levels and increased SBP levels were independent predictors of the presence of multi-organ involvement. The human and animal studies show that the relationship between vitamin D and blood pressure is the result of increased RAAS activation (20-22). Besides, VDD is associated with increased parathormone, which can cause hypertension with both hypertrophy and fibrosis of endothelial smooth muscle cells and increased endothelial calcification (23). Increased parathormone levels result in higher BP (24). Continuous BP load affects the left heart, resulting in left ventricular hypertrophy (25). These direct and indirect effects of vitamin D suggest that it may play a role in myocardial remodeling manifested by cardiac hypertrophy and interstitial fibrosis, which are important indicators of heart failure in hypertension (26).

From VDS to VDSD, CIMT, which is an indicator of subclinical endothelial dysfunction, and LVMI, which is an indicator of hypertrophy were gradually increased. Recent studies show that VDD is an important factor in endothelial dysfunction and cardiac hypertrophy, addition to BP (8, 27, 28). Cardiac hypertrophy is frequently observed in hypertension patients with 25(OH)D deficiency (29). However, endothelial dysfunction is an important change due to hypertensive damage in the central and peripheral arteries, and it precedes cardiac hypertrophy in hypertensive patients and is an important predictor of cardiac hypertrophy (30). This may explain the stronger association between CIMT and Vitamin D levels compared to other TOD indicators in current findings. Besides, the relationship between endothelial dysfunction and cardiac hypertrophy plays an important role in the development or progression of renal damage (31). Renal damage due to hypertension is based on increased urinary albumin excretion as a result of increased intra-glomerular pressure due to decreased kidney functions (32). We found a negative correlation between Vitamin D and microalbuminuria and proteinuria, which is an indicator of early kidney damage. Therefore, vitamin D levels were directly or indirectly related from endothelial dysfunction to heart and kidney damage. This may be due to the relationship between Vitamin D and RAAS activation.

Recent evidence suggests that the Vitamin D plays a role in the inflammatory response (1). We found a negative correlation between Vitamin D and NLR levels in hypertensive patients. In addition, these two parameters were independent predictors of both TOD and multi-organ involvement. Previous hypertensive studies have shown a positive correlation between NLR levels and the presence of TOD (33, 34). Hypertensive experimental studies have shown that vitamin D depletion increases natriuretic peptides and neutrophil activation (5, 35). In spontaneously hypertensive rats, Vitamin D3 deficiency induced neutrophil ROS production, increased micronucleus formation and was associated with induced DNA damage (35). This suggests that Vitamin D participates in the inflammatory response by playing a role in the adaptive and innate immune system in hypertensive organ damage. The negative relationship between vitamin D and CRP and NLR levels supports this hypothesis. Therefore, VDD may be associated with different mechanisms such as RAAS activation and immune-inflammatory response in hypertensive organ involvement, and the coexistence of these relationships may cause more organ involvement. A gradual increase in CRP and NLR levels was detected in patients with multi-organ involvement, but a gradual decrease in vitamin D was detected.

In the current study, we found that the relationship between Vitamin D deficiency and TOD continues regardless of disease duration and anti-hypertensive treatments. Although the effects of traditional risk factors were eliminated in most of the studies, the duration of the disease and the effects of anti-hypertensive drugs were not taken into account. Since the majority of hypertensive patients are in the advanced age group, a decrease in vitamin D levels can be observed (36). The duration of the disease increases with increasing age. For this reason, increasing disease duration may decrease in vitamin D due to aging and increase the severity of TOD due to the rate of atherosclerosis. On

the other hand, considering the effect of Vitamin D on RAAS, the effectiveness of anti-hypertensive treatments may be affected (37, 38). Therefore, in hypertensive patients with VDD, Vitamin D supplementation can reduce the probability of TOD, slow down or prevent the atherosclerotic process, regardless of disease duration or anti-hypertensive drugs. Randomized controlled prospective studies are needed to support this.

Our study has some important limitations. Firstly, 1,25(OH)2D levels of patients could not be measured due to the retrospective study design. Circulating vitamin D levels are transmitted by the VDR signal. Therefore, measured vitamin D levels do not reflect the circulating active form, 1,25(OH)2D. This may be insufficient to fully elucidate the physiological effect of Vitamin D on the development of TOD. Another important limitation is that a marker that directly indicates endothelial damage has not been studied, so it does not provide conclusive evidence between endothelial damage and vitamin D deficiency. In addition, the seasonal variation of vitamin D and the low number of our patients are among our other important limitations.

CONCLUSION

In hypertensive patients, a decrease in vitamin D levels is associated with an increase in TOD indicators. The risk of developing TOD and multi-organ involvement is higher in vitamin D deficiency. Considering the high prevalence of multi-organ involvement in the case of vitamin D deficiency, it is thought that the atherosclerotic process may accelerate. Vitamin D supplements may be beneficial in hypertensive organ damage, regardless of disease duration and anti-hypertensive treatments.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Non-interventional Clinical Research Ethics Committee (Date: 29.06.2022, Decision No: 2022.06.21).

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. Jeong HY, Park KM, Lee MJ, Yang DH, Kim SH, Lee SY. Vitamin D and hypertension. Electrolyte Blood Press 2017; 15: 1-11.
2. Mehta V, Agarwal S. Does Vitamin D Deficiency Lead to Hypertension? Cureus 2017; 9: e1038.
3. Ulu SM, Ulasli A, Yaman F, Yaman G, Ozkececi G, Yuksel S. The relationship between vitamin D and PTH levels and cardiovascular risk in the elderly hypertensives. Clin Exp Hypertens 2014; 36: 52-7.
4. Lawler PR, Hiremath P, Cheng S. Cardiac target organ damage in hypertension: insights from epidemiology. Curr Hypertens Rep 2014; 16: 446.
5. Andersen LB, Przybyl L, Haase N, et al. Vitamin D depletion aggravates hypertension and target-organ damage. J Am Heart Assoc 2015; 4: e001417.
6. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and endothelial function. Nutrients 2020; 12: 575.
7. Manrique C, Lastra G, Gardner M, Sowers JR. The renin angiotensin aldosterone system in hypertension: roles of insulin resistance and oxidative stress. Med Clin North Am 2009; 93: 569-82.
8. Kuloglu O, Gur M, Seker T, et al. Serum 25-hydroxyvitamin D level is associated with arterial stiffness, left ventricle hypertrophy, and inflammation in newly diagnosed hypertension. J Investig Med 2013; 61: 989-94.
9. Yilmaz F, Sozel H. Relationship between 25-hydroxyvitamin D and microalbuminuria in patients with newly diagnosed essential hypertension. Clin Exp Hypertens 2021; 43: 217-22.
10. Lupoli R, Vaccaro A, Ambrosino P, Poggio P, Amato M, Di Minno MN. Impact of Vitamin D deficiency on subclinical carotid atherosclerosis: a pooled analysis of cohort studies. J Clin Endocrinol Metab 2017; 102: 2146-53.
11. Karki A, Vaidhya S, Kunwar D, Kunwar R. Vitamin D Deficiency among Patients Presenting to Outpatient Department of Medicine of a Tertiary Care Centre: A Descriptive Cross-sectional Study. JNMA J Nepal Med Assoc 2022; 60: 465-8.
12. Meehan M, Penckofer S. The Role of Vitamin D in the Aging Adult. J Aging Gerontol 2014; 2: 60-71.
13. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39: 3021-104.
14. Perrone-Filardi P, Coca A, Galderisi M, et al. Noninvasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: a consensus article from the European Association of Cardiovascular Imaging, the European Society of Cardiology Council on Hypertension and the European Society of Hypertension. J Hypertens 2017; 35: 1727-41.
15. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-30.
16. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986; 57: 450-8.
17. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2007; 23: 75-80.
18. Liu Y, Shi L, Lin Y, et al. Relationship between serum 25-hydroxyvitamin D and target organ damage in children with essential hypertension. J Hum Hypertens 2022; 36: 604-9.
19. Vimaleswaran KS, Cavadino A, Berry DJ, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. Lancet Diabetes Endocrinol 2014; 2: 719-29.

20. McMullan CJ, Borgi L, Curhan GC, Fisher N, Forman JP. The effect of vitamin D on renin-angiotensin system activation and blood pressure: a randomized control trial. J Hypertens 2017; 35: 822-9.
21. Vaidya A, Williams JS. The relationship between vitamin D and the renin-angiotensin system in the pathophysiology of hypertension, kidney disease, and diabetes. Metabolism 2012; 61: 450-8.
22. Forman JP, Williams JS, Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. Hypertension 2010; 55: 1283-8.
23. Ke L, Mason RS, Kariuki M, Mpofu E, Brock KE. Vitamin D status and hypertension: a review. Integr Blood Press Control 2015; 8: 13-35.
24. Fisher SB, Perrier ND. Primary hyperparathyroidism and hypertension. Gland Surg 2020; 9: 142-9.
25. Yildiz M, Oktay AA, Stewart MH, Milani RV, Ventura HO, Lavie CJ. Left ventricular hypertrophy and hypertension. Prog Cardiovasc Dis 2020; 63: 10-21.
26. Tomek J, Bub G. Hypertension-induced remodelling: on the interactions of cardiac risk factors. J Physiol 2017; 595: 4027-36.
27. Seker T, Gur M, Ucar H, et al. Lower serum 25-hydroxyvitamin D level is associated with impaired myocardial performance and left ventricle hypertrophy in newly diagnosed hypertensive patients. Anatol J Cardiol 2015; 15: 744-50.
28. Carrelli AL, Walker MD, Lowe H, et al. Vitamin D deficiency is associated with subclinical carotid atherosclerosis: the Northern Manhattan study. Stroke 2011; 42: 2240-5.
29. Fallo F, Catena C, Camozzi V, et al. Low serum 25-hydroxyvitamin D levels are associated with left ventricular hypertrophy in essential hypertension. Nutr Metab Cardiovasc Dis 2012; 22: 871-6.
30. Budzyn M, Gryszczynka B, Boruczkowski M, et al. The potential role of circulating endothelial cells and endothelial progenitor cells in the prediction of left ventricular hypertrophy in hypertensive patients. Front Physiol 2019; 10: 1005.
31. Poulikakos D, Ross L, Recio-Mayoral A, et al. Left ventricular hypertrophy and endothelial dysfunction in chronic kidney disease. Eur Heart J Cardiovasc Imaging 2014; 15: 56-61.
32. Mule G, Castiglia A, Cusumano C, et al. Subclinical kidney damage in hypertensive patients: A renal window opened on the cardiovascular system. focus on microalbuminuria. Adv Exp Med Biol 2017; 956: 279-306.
33. Sevencan NO, Ozkan AE. Associations between neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, albuminuria and uric acid and the estimated glomerular filtration rate in hypertensive patients with chronic kidney disease stages 1-3. Arch Med Sci 2019; 15: 1232-9.
34. Wang H, Hu Y, Geng Y, et al. The relationship between neutrophil to lymphocyte ratio and artery stiffness in subtypes of hypertension. J Clin Hypertens (Greenwich) 2017; 19: 780-5.
35. Machado Cda S, Venancio VP, Aissa AF, et al. Vitamin D3 deficiency increases DNA damage and the oxidative burst of neutrophils in a hypertensive rat model. Mutat Res Genet Toxicol Environ Mutagen 2016; 798-799: 19-26.
36. Gallagher JC. Vitamin D and aging. Endocrinol Metab Clin North Am 2013; 42: 319-32.
37. Legarth C, Grimm D, Wehland M, Bauer J, Kruger M. The impact of Vitamin D in the treatment of essential hypertension. Int J Mol Sci 2018; 19: 455.
38. Sheikh V, Mozaianimonfared A, Gharakhani M, Poorolajal J, Ph D. Effect of vitamin D supplementation versus placebo on essential hypertension in patients with vitamin D deficiency: a double-blind randomized clinical trial. J Clin Hypertens (Greenwich) 2020; 22: 1867-73.

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A radiological and clinical overview of the effects of COVID-19 on the male reproductive system: micro V Doppler, spermiogram and international erectile function form survey results

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ABSTRACT

Introduction: Micro V Doppler is a different technique from the conventional Doppler US method, which reveals the small vessel structure developed in recent years. We planned to reveal whether there are significant difference between spermiogram test, scrotal US, Micro V Doppler and international erectile function form questionnaire results between patients who had recently COVID-19 and the control group.

Material and Method: Our study included 45 patients who had recently had COVID-19 infection, and 45 control patients. Spermiogram test, scrotal US, Micro V Doppler and erectile dysfunction score, orgasmic function score, sexual desire score, sexual satisfaction score, and general satisfaction scores were evaluated for our patients and control groups included in our study.

Results: On scrotal US, there was no sequelae in the parenchyma in all patients (n=45, 100%) who had experienced COVID-19. When the spermiogram tests of the control group and our patients with COVID-19 infection were compared, the presence of oligozoospermia, leukocytospermia and other abnormal positive findings was similar between the two groups ($p>0.005$). Micro V Doppler findings of the control group and our patients who did not have COVID-19 infection were similar. Sexual Desire and sexual satisfaction scores of patients with COVID-19 were significantly lower than the control group without COVID-19 infection ($p<0.05$), however, there was no significant difference between the groups in terms of erectile dysfunction, orgasmic function and overall satisfaction.

Conclusion: COVID-19 does not cause a permanent significant difference in the morphological structure of testicles on Micro V Doppler examination and spermiogram tests. Sexual desire and sexual satisfaction scores are decreased in patients who had recently COVID-19.

Keywords: Doppler, micro V Doppler, COVID-19, testis

INTRODUCTION

The COVID-19 virus (SARS-CoV-2) is known to have important effects on vital organs such as the heart, lungs, kidneys, and brain, but its physical and psychological effects on general reproductive system in men are not well known (1). The brain and testicles are two important structures that are in close relationship with each other via gonadotropins and sex steroid hormones (2). There are studies discussing that COVID-19 may affect the hypothalamus and decrease gonadotropins and testosterone, and there may be variability in sexual desire and satisfaction of patients. In addition, it has been reported in these studies that hyperthermia caused by systemic infection causes an increase in leukocytes and an inflammatory response in the testicular tissue (2,3).

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Micro V examination is a newly developed technology which evaluate the slow flow of microvascular structures and discriminated from tissue motion artefact. Micro V benefit from the rapid frame rates, thus clutter signals are suppressed and slow flow of microvessel can be exracted (4).

We planned to reveal whether there are significant difference between spermiogram test, scrotal US, Micro V Doppler and international erectile function form (IIEF) questionnaire results between patients who had recently COVID-19 and the control group. We contribute to the literature as one of the pioneering studies that perform Micro V Doppler, and IIEF evaluation in patient groups with COVID-19.

MATERIAL AND METHOD

The study was conducted with the permission of Başakşehir Çam and Sakura Research Hospital Non-invasive Clinical Researches Ethics Committee (Date: 07.02.2021, Decision No: 2021.05.100). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

General Data

Our study included 45 patients between the ages of 18-55 who applied to the outpatient clinic and had COVID-19 infection in the last 3 months, and 45 patients who did not have COVID-19 infection and applied to the polyclinic. Patients with varicocele, previous inguinal hernia operation, systemic disease such as malignancy, diabetes mellitus, hypertension, those with a history of testicular tissue damage due to other reasons in previous scrotal US controls, and those with a history of torsion were excluded from the study. Our patients included in our study were evaluated for spermiogram test, scrotal US, Micro V Doppler and IIEF erectile dysfunction score, orgasmic function score, sexual desire score, sexual satisfaction score, and general satisfaction scores. The spermiogram tests of all our patients were examined and the presence of oligozoospermia, leukocytospermia and other abnormal positive findings (motility, morphology) were noted. When the spermiogram tests of our patients in the control group who did not have COVID-19 were compared with those in the patients who had COVID-19 infection, it was evaluated whether there was a significant difference between the two groups in terms of these parameters.

Micro V Doppler Examination

In the scrotal US (Esaote MayLab 9 Xp device using a 5-14 MHz linear transducer probe) examination, both testicular parenchyma, volumes and color Doppler vascularity were examined, and patients with abnormal conditions were noted. Then, Micro V Doppler examination, which shows the microvascular bed and has its own special software at high frame rate, was started. Testicular parenchyma was examined with Micro V examination, focal damage area in blood supply in micro vascular structures and decrease in general blood supply were evaluated. We used the grading system created by Arslan et al. (5) which is a grading for imaging systems using high fram rate and used for imaging the microvascular bed. According to this visual system, Grade 1 was classified as several punctate blood supplies and minimal vascularity, on Micro V Doppler. The vascularity without anarchic vascular structures and no more than two linear microvascular signals are accepted as grade 2. In grade 3 vascularity, more than two vascular structures are seen. Multiple irregularly shaped and curved microvascular structures in the center and periphery of the parenchyma is defined as grade 4 (5, 6).

The use of simplified International Index of Erectile Function (IIEF-5)

The IIEF-5 questionnaire was used to evaluate the sexual quality of life of the patients. Accordingly, our patients were asked to answer a 15-question questionnaire on the form so that we could evaluate erectile and orgasmic functions (max points 30 and 10), sexual desire (max points 10), satisfaction with intercourse(max points 15) and overall sexual satisfaction(max points 10) (7,8). In one of our patients who could get 30 points in total, if the score was 25 or less, the diagnosis of erectile dysfunction was established.

Statistical Analysis

All statistical analysis was performed using R 3.6.0 (https://www.r-project.org). Shapiro-Wilk's normality test and Q-Q plots were used to check the normality of the data, and also Levene's test was used to check the homogeneity of groups' variances. Categorical data were described as numbers (n) and percentages, numerical data were expressed as mean±standard deviation. The McNemar test was used to determine if there were difference in proportions between pre and post-disease of the patients with COVID-19 in terms of oligozoospermia, leucocytospermia and anormal positive findings. Chi-square test was used to examine the association between study groups and Micro V Doppler findings. In addition to, independent samples t-tests were used to compare the differences between COVID-19 patients and healthy controls with regard to IIEF score, orgasmic function score, sexual desire score, intercourse satisfaction score and overall satisfaction score. A value of p less than 0.05 was considered as statistically significant.

RESULTS

The mean age of 45 patients was 30.60±7.32 (range: 17-49 years), right testis volume mean 13.12±0.82 cc (range: 11-15 cc), left testis volume mean 12.74±0.95 cc (range:

11-16 cc). No sequelae change was observed within the parenchyma in all patients who had COVID-19. When the spermiogram tests of the patients who had COVID-19 and the healthy control group were compared; oligozoospermia, leucocytospermia and abnormal positive findings are given in **Table 1**. The presence of oligozoospermia, leucocytospermia and abnormal positive findings in the past and post-infection of the patients were similar (p>0.05). The differences between the Micro V Doppler findings, IIEF score and subheadings of patients with COVID-19 and healthy controls were examined. Micro V Doppler findings of the patients with COVID-19 and the control group were similar (p=0.158) (**Figure 1**). The IIEF Sexual Desire (5.16±1.19 vs. 8.62±1.27, Mean diff.= 3.47, [95% CI, 2.95-3.98], t(88)= 13.40, p<.001, Cohen's d=2.83) and Sexual Satisfaction (10.60±1.50 vs. 11.82±1.30, Mean diff.= 1.22, [95% CI, 0.63-1.81], t(88)= 4.13, p<.001, Cohen's d=0.87) scores of patients with COVID-19 were significantly lower in the group of patients with COVID-19 infection. However, there was no significant difference between the groups in terms of erectile dysfunction, orgasmic function, and general satisfaction (all p-value>.05) (**Graphic 1**).

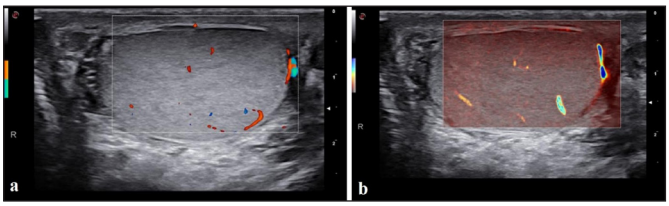


Figure 1. 25 year-old patient who had formerly known COVID-19, (a) on color Doppler image (b) on Micro V Doppler imaging grade 2 parenchymal vascularity is seen.

Table 1. Spermiogram test findings of patients who had recently COVID-19 and control

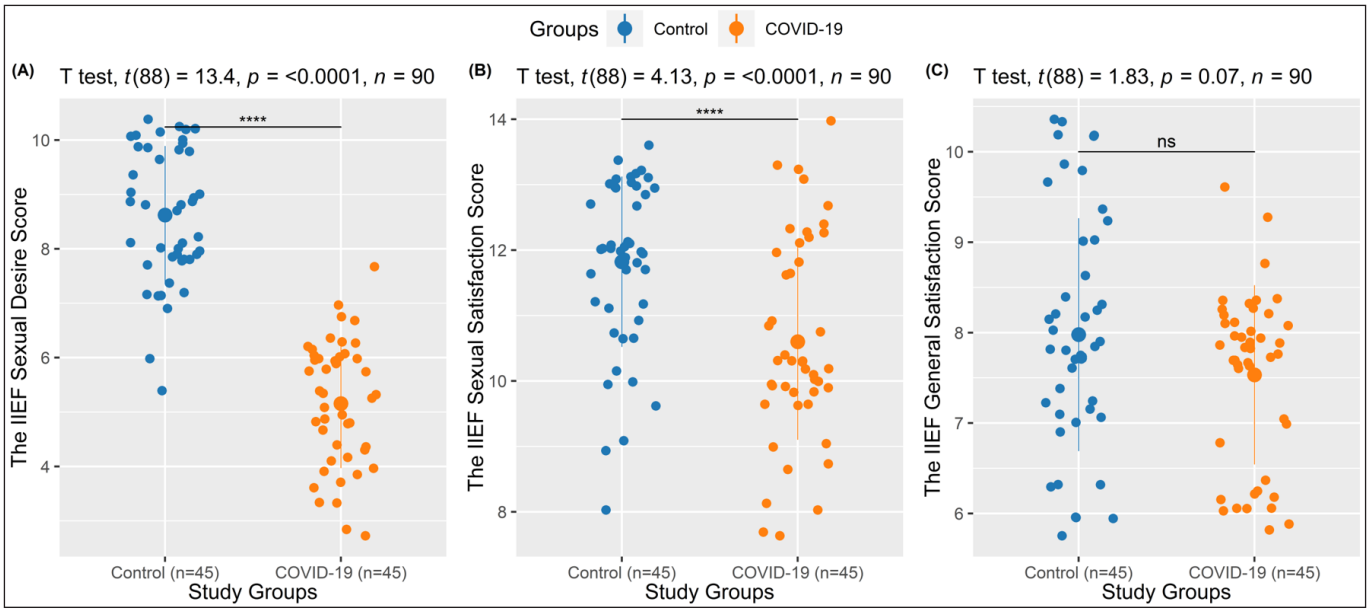
Parameters	Patients who had not COVID-19 (control)		Patients who had recently COVID-19		p value
	Positive findings	Negative findings	Positive findings	Negative findings	
Oligozoospermia	1 (2.2)	44 (97.8)	2 (4.4)	43 (95.6)	0.317
Leucocytospermia	2 (4.4)	43 (95.6)	2 (4.4)	43 (95.6)	>.999
Abnormal positive findings	1 (2.2)	44 (97.8)	2 (4.4)	43 (95.6)	0.317

Data were described as numbers of patients (n) and percentages (%). p-value calculated using McNemar chi-square test.

DISCUSSION

In this prospective study, when the spermiogram tests of the patients who had COVID-19 and the healthy control group were compared; oligozoospermia, leucocytospermia and abnormal positive findings were similar (p=.317, p>.999 and p=.317, respectively). When we compared the two groups, no difference was found in terms of Micro V Doppler. Sexual Desire and Sexual Satisfaction scores were significantly lower in the patients with post COVID-19 infection (p<0.05).

It has been reported that ACE2 receptors are found in the kidneys, Sertoli and leyding cells, and spermatogonia within the genitourinary system. SARS-CoV virus uses ACE2 receptors to enter cells (9). Honggang et al. (10) reported that severely ill-deceased COVID-19 patients in whom they performed postmortem examination showed thinning of the seminiferous epithelium thickness and a significant increase in the number of apoptotic cells at this level. They detected oligospermia in semen samples and thus reported that COVID-19 directly affects the



Graphic 1. Comparisons of International Index of Erectile Function (IIEF) Questionnaire between COVID – 19 patients and healthy controls. Data were presented as mean with standard deviations *: a significant difference between groups, ns: not significant. Error–plots, which show the (A) The IEFF Sexual Desire score, (B) The IEFF Sexual Satisfaction score in the COVID–19 patients and healthy controls. Significantly decreased these scores were noted in the COVID–19 patients when compared with the healthy controls. However, (C) A error–plot, which show the IEFF General Satisfaction score in the groups, and there was no statistically significant difference between COVID–19 patients and healthy controls.

male reproductive system. Xu et al. (11) reported that T-lymphocytes and macrophages attack the testicular parenchyma as a mechanism, which causes viral-associated epididymorchitis. Another theory is that abnormal amounts of IgG precipitates are observed in the seminiferous tubules after macrophage and T lymphocyte attack, and therefore, secondary autoimmune response to the viral infection may develop and orchitis may develop due to autoimmune (11). Bridwell et al. (12) reported two orchitis case caused by SARS-CoV and they also suggested that it would be beneficial to follow-up fertility in these patients. Another study reported that imaging these patients and getting control with spermiogram test is important for us to understand whether the effects are reversible (10). In these studies, spermiogram tests and scrotal Doppler US were performed in very early periods. And in the acute process, significant inflammation, significant increase in vascularity in Doppler and deterioration in spermiogram were detected. We think that the reason why there were no significant radiological (Micro V) or laboratory differences between the two groups in our study, unlike the literature, is due to the fact that the examination was performed at a later time. Thus, we think that the effects are reversible. Classical color and power Doppler algorithms perceive the slow flow of micro vascular structures as clutter and cannot distinguish this slow flow from the mechanical movement of the background tissue (5). For this reason, they also delete the slow flow which considered as an artifact. Doppler methods have been developed by different companies, which use the recently developed high frame rate and can see microvascular structures with its unique algorithm rather than large-medium diameter vascular structures (Esoate: Micro V Doppler and Toshiba: Superb microvascular imaging) (5,6). There are publications reporting that microvascular imaging techniques are extremely successful in superficial organs such as testis and breast in examinations performed with a lineer probe (13). Fu et al. (13) conducted a study which evaluates the clinical applications of microvascular imaging methods. They reported that angiogenesis is very important in the mechanism of inflammation and metastasis of diseases, and therefore, microvascular imaging methods may have an important role in demonstrating the course and permanent effects of diseases. According to Visalli et al. (14) found that microvascular imaging techniques can detect vascularization in healthy testicles which have no signal on power Doppler. In a recent study evaluating active synovitis by using microvascular imaging techniques; they reported Micro V Doppler can demonsrate low-grade inflammation more succesfully compared to color Doppler (15). Moreover, the degree of visuliazed slow blood flow on microimaging methods reflected the inflammatory process. As the severity of vascularity detected on microimaging examination increase, symptoms and magnetic resonance imaging findings also increase. According to Ayaz et al. (16) conducted a large-scale study in which they examined the testicles of newborns. They found that Micro V Doppler provide additional information about the structure distribution and number of microvessels.

There are current studies reporting some changes in the hormone profile in men with COVID-19 (17,18). It has been reported that these patients have increased luteinizing hormone, follicle-stimulating hormone, prolactin and decreased estradiol, progesterone, and testosterone levels. Tian et al. (18) reported that SARS-CoV RNA was detected in acidophilic cells of the pituitary. And thus, it has been reported that COVID-19 may have some effects on the hypothalamus and pituitary gland. It may cause abnormal sex hormone levels by affecting the hyphthalamo-pituitary axis, thus leading to sexual dysfunction (18). In our study, the sexual desire and sexual satisfaction scores were significantly lower in the patient group with COVID-19 infection. We think that another important reason why the disease causes a decrease in sexual desire without physically creating an erectile dysfunction or without significant changes in the testicular parenchyma in Micro V examination may be the significant mental stress experienced during COVID-19. Kaya et al. (19) conducted a study evaluating the effect of COVID-19 on sexual dysfunction in women. And they reported that the frequency of sexual intercourse and sexual satisfaction in women decreased after COVID-19 disease. Cito et al. (20) reported that during COVID-19 disease couple has more chance to improve their sexuality thanks to quarantine. But they also found that a decrease in the number of sexual intercourse was observed in the patients included in the study, which may be due to the decrease in psychological stimuli and emotional stress. In another study, it was found that the satisfaction score decreased in patients after COVID-19 (19).

There were some limitations in our study. First, we did not examine the pre- and post-disease conditions of the patient group. We compared them with the patient who did not have recently COVID-19. And patients with COVID-19 were not divided into groups as severe and mild. In the literature, patients with oligospermia on spermiogram were generally those with severe or lethal disease. Secondly, we had relatively small sample size. Interobserver variability was not evaluated in Micro V doppler examinations.

CONCLUSION

COVID-19 does not cause a permanent significant difference in the morphological structure of testicles on Micro V Doppler examination and spermiogram tests.

Sexual desire and sexual satisfaction scores are decreased in patients who had recently COVID-19. Decreased sexual desire and sexual satisfaction scores without any impairment in functional and morphological findings, it may be an associated with anxiety created by the psychological dimension of COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of Başakşehir Çam and Sakura Research Hospital, Non-invasive Clinical Researches Ethics Committee (Date: 07.02.2021, Decision No: 2021.05.100).

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. Aitken RJ. COVID-19 and human spermatozoa-Potential risks for infertility and sexual transmission? Andrology 2021; 9: 48-52.
2. Selvaraj K, Ravichandran S, Krishnan S, Radhakrishnan RK, Manickam N, Kandasamy M. Testicular atrophy and hypothalamic pathology in COVID-19: possibility of the incidence of male infertility and HPG axis abnormalities. Reprod Sci 2021; 28: 2735-42.
3. Ardestani Zadeh A, Arab D. COVID-19 and male reproductive system: pathogenic features and possible mechanisms. J Mol Histol 2021; 52: 869-78.
4. Mack LM, Mastrobattista JM, Gandhi R, Castro EC, Burgess APH, Lee W. Characterization of placental microvasculature using superb microvascular imaging. J Ultrasound Med 2019; 38: 2485-91.
5. Arslan FZ, Altunkeser A, Körez MK, Aksoy N, Bayramoğlu Z, Karagülle M. The importance of superb microvascular imaging for the differentiation of malignant breast lesions from benign lesions. Eur J Breast Health 2021; 18: 48-54.
6. Karagülle M, Arslan FZ, Şimşek S, et al. Investigation of the effectiveness of microvascular Doppler ultrasound and Q-Pack in the discrimination of malign thyroid nodules from benign. Ultrasound Q 2022.
7. Rhoden EL, Telöken C, Sogari PR, Vargas Souto CA. The use of the simplified International Index of Erectile Function (IIEF-5) as a diagnostic tool to study the prevalence of erectile dysfunction. Int J Impot Res 2002; 14: 245-50.
8. International Index of erectile function. Patient questionnaire. Available online: https: //www.baus.org.uk/_userfiles/pages/files/Patients/Leaflets/iief.pdf
9. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565-74.
10. Li H, Xiao X, Zhang J, et al. Impaired spermatogenesis in COVID-19 patients. EClinicalMedicine 2020; 28: 100604.
11. Xu J, Qi L, Chi X, et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). Biol Reprod 2006; 74: 410-6.
12. Bridwell RE, Merrill DR, Griffith SA, et al. A coronavirus disease 2019 (COVID-19) patient with bilateral orchitis. Am J Emerg Med 2021; 42: 260.e3-260.e5.
13. Fu Z, Zhang J, Lu Y, et al. Clinical applications of superb microvascular imaging in the superficial tissues and organs: a systematic review. Acad Radiol 2021; 28: 694-703.
14. Visalli C, Vinci SL, Mondello S, et al. Microvascular imaging ultrasound (MicroV) and power Doppler vascularization analysis in a pediatric population with early scrotal pain onset. Jpn J Radiol 2022; 40: 192-201.
15. Oo WM, Linklater JM, Bennell KL, et al. Superb microvascular imaging in low-grade inflammation of knee osteoarthritis compared with power Doppler: clinical, radiographic and MRI relationship. Ultrasound Med Biol 2020; 46: 566-74.
16. Ayaz E, Ayaz M, Önal C, Yıkılmaz A. Seeing the unseen: evaluating testicular vascularity in neonates by using the superb microvascular imaging ultrasound technique. J Ultrasound Med 2019; 38: 1847-54.
17. Wang Z, Xu X. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 Infection in spermatogonia, leydig and sertoli cells. Cells 2020; 9: 920.
18. Tian Y, Zhou LQ. Evaluating the impact of COVID-19 on male reproduction. Reproduction 2021; 161: R37-R44.
19. Kaya Y, Kaya C, Tahta T, Kartal T, Tokgöz VY. Examination of the effect of COVID-19 on sexual dysfunction in women. Int J Clin Pract 2021; 75: e13923.
20. Cito G, Micelli E, Cocci A, et al. The impact of the COVID-19 quarantine on sexual life in Italy. Urology 2021; 147: 37-42.

Original Article

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Oxidative stress indicators during the course of acute graft versus host disease

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ABSTRACT

Aim: This prospective study aimed to observe the changes in oxidative stress indicators, including total anti-oxidant status (TAS), total oxidant status (TOS), paraoxanase-1 (PON1), total thiol (TT), native thiol (NT), disulphide (DS) and nitric oxide (NO) levels from sequential blood samples obtained during a de-novo episode of acute graft versus host disease (aGvHD) and evaluate their association with disease severity and the risk of steroid resistant disease.

Material and Method: Sequential patients who underwent an allogeneic stem cell transplantation (ASCT) in our unit and subsequently developed a de-novo episode of aGvHD between January 2022 and May 2022 were included in case they gave informed consent. All patients were started high dose (2 mg/kg/day) methylprednisolone as institutional standard first-line treatment of aGvHD as soon as the clinical diagnosis is evident. All episodes were confirmed simultaneously with gastrointestinal (GI) endoscopy and/or skin biopsies. TAS, TOS, PON1, TT, NT, DS and NO were studied from blood samples collected on days 0, +3 and +7 of steroid treatment. Demographic characteristics, diagnoses, donor type, GvHD prophylaxis, stage and grade of aGvHD, performance status (PS), the presence of cytomegalovirus (CMV) reactivation and response to steroid therapy were also noted.

Results: A total of 15 cases was included. The median age was 49 (23-77). Males constituted 60.0% (n=9). The most frequent diagnosis and donor type were acute leukemia (53.3%, n=8) and matched related donor (46.7%, n=7), respectively. High grade aGvHD with Glucksberg grading and International Bone Marrow Transplant Registry severity index (IBMTR-SI) included 53,3% (n=8) and 86.7% (n=10) of cases, respectively. Non-responders (20.0%, n=3) significantly had advanced stage GI involvement, higher grade of aGvHD with Glucksberg grading and IBMTR-SI, and lower PS (p=0.005, p=0.04, p=0.006, and p=0.02, respectively). The changes in TAS, TOS, PON1, TT, NT, DS and NO levels on days 0, +3 and +7 of steroid treatment were not significant. Median PON1 levels on days 0, +3 and +7 of steroid treatment were significantly lower among non-responders ($p<0.01$, $p<0.02$, and $p=0.03$, respectively).

Conclusion: Steroid resistant aGvHD is an important cause of morbidity and mortality after ASCT. Advanced stage GI involvement and higher total grade of aGvHD is associated with steroid resistance. Lower PON1 levels may be employed as an early indicator of steroid resistance and thus may allow for the early start of more aggressive therapies. Cut-off values and possible confounders should be investigated in further studies.

Keywords: Oxidative stress, graft versus host disease, paraoxanase

INTRODUCTION

Acute graft versus host disease (aGvHD) is one of the leading causes of morbidity and mortality after allogeneic stem cell transplantation (ASCT), which is a curative treatment for various hematologic malignancies (1). The treatment for aGvHD should be promptly started after proper diagnosis, staging and grading. Staging and grading of aGvHD are made according to the severity and extent of organ involvement, which mainly include skin, gastrointestinal (GI) tract and liver. The two most commonly used grading systems include the Glucksberg grading (I to IV) and the International Bone Marrow Transplant Registry severity index (IBMTR-SI) (A to D) (2,3). The first-line treatment of aGvHD depends mainly on the use of high dose systemic glucocorticoids (4-6). However, grade I aGvHD, which includes only the limited involvement of skin, may be treated with topical steroids. The progression of grade I aGvHD to grade II can be prevented with systemic glucocorticoid treatment, whereas it has no effect on progression to grade III-IV disease (7). Methylprednisolone at doses of 2 mg/kg/day is generally the standard choice of therapy. Lower dose treatment (i.e.; 1 mg/kg/day) may also be effective in selected cases (8). Systemic steroids are associated with complete response rates of 25 to 40 percent and more than half of the patients relapse after initial response (4). Steroid resistant aGvHD (SR-aGvHD) is defined as progression of aGvHD by day +5 or a lack of response by day +7 of glucocorticoid treatment (9). The prognosis of SR-aGvHD is still dismal despite promising second-

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line treatments including extracorporeal plasmapheresis (ECP), ruxolitinib, etanercept and many others (9-11).

Donor T-cells play a pivot role in the pathogenesis of aGvHD. After the presentation of recipient antigens to donor T-cells during the ASCT process, donor T-cell activation and consequent development of an immune response against recipient's tissues take place. During this response an increased expression of pattern recognition receptors on antigen-presenting cells, a massive inflammatory cytokine secretion [mainly, tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6] and release of free radicals and oxidative stress products are observed (12, 13). There has been continuing efforts to define various diagnostic and prognostic markers for aGvHD, which yielded inconclusive results (14).

This prospective study aimed to observe the changes in oxidative stress indicators, including total anti-oxidant status (TAS), total oxidant status (TOS), paraoxanase-1 (PON1), total thiol (TT), native thiol (NT), disulphide (DS) and nitric oxide (NO) levels from sequential blood samples obtained during a de-novo episode of aGvHD and evaluate their association with disease severity and the risk of SR-aGvHD.

MATERIAL AND METHOD

The study was carried out with the permission of the Medicana Hospital Clinical Research Ethics Committee (Date: 24.11.2021, Decision No: BŞH-2022/39). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Sequential patients who underwent an ASCT in our unit and subsequently developed a de-novo episode of aGvHD between January 2022 and May 2022 were included in case they gave informed consent. aGvHD is classified into three subgroups according to the time of presentation and presenting features: 1) classic aGvHD-clinical features of aGvHD within 100 days of ASCT; 2) persistent, recurrent, late onset aGvHD-clinical features of aGvHD occurring beyond 100 days after ASCT; 3) overlap syndrome-clinical features of both aGvHD and chronic aGvHD at any time after ASCT (15,16). aGVHD was staged and graded according to Glucksberg and IBMTR-SI criteria. All patients were started high dose (2 mg/kg/day) methylprednisolone as institutional standard first-line treatment of aGvHD as soon as the clinical diagnosis is evident. All episodes were confirmed simultaneously with gastrointestinal (GI) endoscopy and/or skin biopsies. Steroid response was evaluated on days +5 and +7 of steroid therapy. We hypothesized that a possible earlier change on day +3 detected before the clinical judgement of steroid resistance may help to predict the response obtained on day 5. We also decided that another sample obtained on day +7 may help us to assess a correlation with the final clinical judgement for steroid resistant disease. In order to predict and to demonstrate a possible correlation with the steroid response, TAS, TOS, PON1, TT, NT, DS and NO were studied from blood samples collected on days 0, +3 and +7 of steroid treatment.

Demographic characteristics, diagnoses, donor type, GvHD prophylaxis, stage and grade of aGvHD, performance status (PS), the presence of concomitant cytomegalovirus (CMV) reactivation and response to steroid therapy were also noted. The study was approved by the local ethics committee of our hospital and all procedures was conducted in accordance with the ethical standards specified in the Declaration of Helsinki.

The analyses of TAS (mmol Trolox Eq/L), TOS (μmol H2O2 Eq/L), PON1 (U/L), TT (μmol/L), NT (μmol/L), NO (μmol/L) were performed with an autoanalyzer (Mindray BS 300) using commercial colorimetric assay kits (Rel Assay Diagnostics®, Turkey) from venous blood samples according to manufacturer's instructions as previously described (17). The concentration of DS, which indicates the amount of reduced thiols, was calculated as half of the difference between TT and NT.

The primary objective of the study was to determine a significant difference in serum levels of TAS, TOS, PON1, TT, NT, DS and NO between steroid responder and non-responders on days 0, +3 and +7 of steroid treatment. The secondary objectives included the observation of longitudinal changes in serum levels of TAS, TOS, PON1, TT, NT, DS and NO on days 0, +3 and +7 of steroid treatment and to define differences in disease and treatment related characteristics between steroid responder and non-responders.

Median, minimum and maximum values were calculated for non-normally distributed continuous variables. Categorical variables were presented as frequencies and percentages. Comparisons between groups were made by Chi-square or Fisher test for categorical variables and Mann-Whitney U test and Kruskal-Wallis test for continuous variables, respectively. Wilcoxon and Friedman's tests were used for the comparison of repeated measures.

Binary logistic regression was used to assess the independent effects of selected parameters on SR-aGvHD. Factors associated with a statistical significance ($p<0.5$) in the univariate analysis were entered via stepwise exclusion into the model. Hosmer Lemeshow goodness of fit statitstics were used to assess a model fit. Multi-collinearity was excluded. Cohort size limited the number of factors in each model to those with suggested association in univariate analysis. Statistical software package IBM SPSS Statistics for Windows version 25.0

(IBM Corp. released 2017. Armonk, NY, USA) was used in all statistical analyses and a 5% type 1 error (two-sided) was considered statistically significant.

RESULTS

A total of 15 patients was included. The median age was 49 (23-77). Males constituted 60.0% (n=9). The most frequent diagnosis and donor type were acute leukemia (53.3%, n=8) and matched related donor (46.7%, n=7), respectively. Most patients received post-transplant cyclophosphamide (PT-Cy)+calcineurin inhibitor (CNI)/sirolimus+mycophenolate mofetil (MMF) for GvHD prophylaxis (n=8, 53.3%). High grade aGvHD with Glucksberg scale (III or IV) and IBMTR-SI (C or D) included 53.3% (n=8) and 66.7% (n=10) of cases, respectively. General characteristics of patients are given in **Table 1**.

Table 1. General characteristics of patients

Age, median (minimum-maximum)	49 (23-77)
Gender, n (%)	
Male	9 (60.0)
Female	6 (40.0)
Diagnosis, n (%)	
Acute myeloblastic leukemia	6 (40.0)
Acute lymphoblastic leukemia	2 (13.3)
Myelodysplastic syndrome	2 (13.3)
Non-Hodgkin lymphoma	2 (13.3)
Aplastic anemia	1 (6.7)
Chronic myelomonocytic leukemia	1 (6.7)
Primary myelofibrosis	1 (6.7)
Donor type, n (%)	
Matched related	7 (46.7)
Matched unrelated	2 (13.3)
Single antigen mismatched unrelated	3 (20.0)
Haploidentical	3 (20.0)
GvHD prophylaxis, n (%)	
CNI+Mtx	3 (20.0)
CNI/sirolimus+MMF	4 (26.7)
PT-Cy+CNI/sirolimus+MMF	8 (53.3)
Glucksberg grade of acute GvHD, n (%)	
I	7 (46.7)
II	1 (6.7)
III	2 (13.3)
IV	5 (33.3)
IBMTR-SI of acute GvHD, n (%)	
A	3 (20.0)
B	7 (46.7)
C	2 (13.3)
D	3 (20.0)
Concommitant CMV reactivation, n (%)	6 (40.0)
Subtype of acute GvHD, n (%)	
Classic	11 (73.3)
Late onset	4 (26.7)

GvHD: graft versus host disease; CNI: calcineurin inhibitor; Mtx: methotrexate; MMF: mycophenolate mofetil; PT-Cy: post-transplant cyclophosphamide; IBMTR: International Bone Marrow Transplant Registry severity index; CMV: cytomegalovirus

Non-responders (20.0%, n=3) significantly had advanced stage GI involvement, higher grade of aGvHD with Glucksberg grading and IBMTR-SI, and lower PS (p=0.005, p=0.04, p=0.006, and p=0.02, respectively) (**Table 2**).

Table 2. Characteristics of patients according to response to steroid therapy

	Non-responder	Responder	P
Gender, n (%)			0.11
Male	3 (100.0)	6 (50.0)	
Female	-	6 (50.0)	
Age, median (min-max)	59 (38-64)	48 (23-77)	0.72
Donor type, n (%			0.73
Haploidentical	1 (33.3)	2 (16.7)	
Single antigen mismatched unrelated	1 (33.3)	2 (16.7)	
Matched related	1 (33.3)	6 (50.)	
Matched unrelated	-	2 (16.7)	
GvHD prophylaxis, n (%)			0.63
CNI+Mtx	1 (33.3)	3 (25.0)	
CNI/sirolimus+MMF	-	3 (25.0)	
PT-Cy+CNI/ sirolimus+MMF	2 (66.7)	6 (50.0)	
Stage of skin involvement, n (%)			0,44
None	-	1 (8.3)	
1	-	5 (41.7)	
2	1 (33.3)	4 (33.3)	
3	1 (33.3)	1 (8.3)	
4	1 (33.3)	1 (8.3)	
Stage of gastrointestinal involvement, n (%)			**0.005**
None	-	7 (58.3)	
1	-	2 (16.7)	
2	-	3 (25.0)	
3	2 (66.7)	-	
4	1 (33.3)	-	
Stage of liver involvement, n (%)			0.11
None	2 (66.7)	11 (91.7)	
1	-	1 (8.3)	
3	1 (33.3)	-	
Performance status, n (%)			**0.02**
<2	-	9 (75.0)	
≥2	3 (100.0)	3 (25.0)	
Glucksberg grade of aGvHD, n (%)			**0.04**
I or II	-	8 (66.7)	
III or IV	3 (100.0)	4 (33.3)	
IBMTR-SI of aGvHD, n (%)			**0.006**
A or B	-	10 (83.3)	
C or D	3 (100.0)	2 (16.7)	
Concommitant CMV reactivation, n (%)	2 (66.7)	4 (33.3)	0.29
Subtype of aGvHD, n (%)			0.24
Classic	3 (100.0)	8 (66.7)	
Late onset	-	4 (33.3)	

aGvHD: acute graft versus host disease; CNI: calcineurin inhibitor; Mtx: methotrexate; MMF: mycophenolate mofetil; PT-Cy: post-transplant cyclophosphamide; IBMTR-SI: International Bone Marrow Transplant Registry severity index; CMV: cytomegalovirus

Median PON1 levels on days 0, +3 and +7; and median NT levels on day +7 of steroid treatment were significantly lower among non-responders (p<0.01, p<0.02, p=0.03, and p=0.03, respectively) (**Table 3**). Median TAS, TOS, PON1, TT, NT, DS and NO levels on days 0, +3 and +7 of steroid treatment were similar between patients having IBMTR-SI low (A or B) and high (C or D) grade aGvHD (**Table 3**). However, there was a tendency for lower NT levels on days 0 and +7 among patients with high IBMTR-SI (C or D) of aGvHD (p=0.07, and p=0.06, respectively) (**Table 3**). The longitudinal changes in TAS, TOS, PON1, TT, NT, DS and NO levels on days 0, +3 and +7 of steroid treatment were not significant (p=0.53, p=0.31, p=0.93, p=1.0, p=0,76, p=0.18, and p=0.91, respectively).

The distribution of age, gender, diagnosis, performance status and steroid response were similar between different donor types (**Table 4**). PT-Cy based GvHD prophylaxis was more frequently used for haploidentical and unrelated donors (p=0.02). aGvHD of Glucksberg grades III to IV were more frequent in ASCTs from haploidentical and single antigen mismatched unrelated donors (p=0.009) (**Table 4**).

A binary logistic regression model including PON-1 levels on day 0 of steroid treatment and aGvHD of Glucksberg grades I/II versus III/IV revealed no significant associations of these parameters on SR-aGvHD (p=0.99 and p=0.99, respectively).

DISCUSSION

SR-aGvHD continues to be a major clinical problem following ASCT. The standard choice of effective second-line treatments also has not been established yet. Thus, the earlier identification of steroid resistant cases may allow for the earlier start of more aggressive first-line therapies, which may provide more favorable outcomes. Ongoing trials evaluating the role of individual biomarkers or their combinations in the diagnosis and prognosis of aGvHD yielded inconsistent results (14, 18).

The pathogenesis of GvHD involves four main phases: 1) conditioning regimen induced tissue injury; 2) activation of host antigen presenting cells; 3) activation of donor T-cells and resultant cytokine storm; 4) end-organ damage due to activated T cells, natural killer (NK) cells, macrophages and cytokines (19). The tissue damage during the early phases of ASCT, which leads to an increased activity of innate immune cells, including neutrophils, macrophages and monocytes, results in release of ROS. This increase in ROS due to neutrophil activity has been linked to an increased GvHD risk (20).

Oxidative stress modifies and regulates the functions of various immune cells (21). It creates inflammatory signals on macrophages via signal transducer/transcription activator 1 (STAT-1), mitogen-activated protein kinases (MAPK) and NF-κB mechanisms and modulate nicotinamide adenine dinucleotide phosphate

Table 3. Changes in studied parameters according to response to steroid therapy and IBMTR-SI

	Non-responders median (minimum-maximum)	Responders median (minimum-maximum)	P	IBMTR-SI A or B median (minimum-maximum)	IBMTR-SI C or D median (minimum-maximum)	P
TAS on day 0	0.91 (0.72-1.21)	0.94 (0.53-1.4)	0.89	0.94 (0.55-1.4)	0.91 (0.53-1.21)	0.81
TAS on day +3	1.41 (0.6-1.55)	1.07 (0.46-1.58)	0.48	1.07 (0.46-1.58)	1.07 (0.6-1.55)	1.0
TAS on day +7	1.57 (1.03-2.11)	0.92 (0.67-1.08)	0.08	0.92 (0.71-1.08)	0.985 (0.67-2.11)	0.51
TOS on day 0	7.59 (3.31-8.09)	3.55 (1.97-13.7)	0.39	3.55 (1.97-13.7)	5.57 (2.46-8.09)	0.71
TOS on day +3	3.97 (2.72-6.65)	2.9 (1.36-9.05)	0.31	3.2 (1.36-9.05)	2.72 (1.42-6.65)	0.74
TOS on day +7	5.23 (2.59-7.87)	2.69 (1.12-6.1)	0.35	2.69 (1.12-6.1)	2.915 (2.07-7.87)	0.51
PON1 on day 0	86 (52-97)	308 (106-420)	**<0.01**	297.5 (106-420)	97 (52-383)	0.39
PON1 on day +3	72 (57-106)	295 (104-458)	**0.02**	294 (104-403)	106 (57-458)	0.55
PON1 on day +7	58 (54-61)	349 (87-427)	**0.03**	332 (87-427)	205 (54-380)	0.34
TT on day 0	270 (247-316)	324 (225-386)	0.11	323.5 (225-386)	282 (247-362)	0.24
TT on day +3	292 (195-374)	312 (207-373)	0.82	305 (207-351)	312 (195-374)	0.55
TT on day +7	243 (157-329)	372 (230-441)	0.24	372 (230-420)	307.5 (157-441)	0.57
NT on day 0	200 (198-220)	239 (103-288)	0.19	248 (103-288)	200 (179-223)	0.07
NT on day +3	215 (183-231)	250 (132-312)	0.48	250 (132-296)	219 (183-312)	0.84
NT on day +7	124 (79-169)	270 (177-317)	**0.03**	270 (180-317)	173 (79-276)	0.06
DS on day 0	25.0 (24.5-58.0)	54.3 (21.5-80.5)	0.31	44.0 (21.5-80.5)	51.5 (24.5-69.5)	0.81
DS on day +3	30.5 (6.0-79.5)	30.5 (14.5-49.5)	1.0	29.5 (14.5-49.5)	30.5 (6.0-79.5)	0.64
DS on day +7	59.5 (39.0-80.0)	48.0 (9.0-92.5)	0.64	38.5 (9.0-92.5)	67.3 (39.0-82.5)	0.13
NO on day 0	13.57 (10.71-19.64)	18.57 (10.71-34.64)	0.28	19.29 (10.71-34.64)	13.93 (10.71-19.64)	0.13
NO on day +3	11.07 (10.36-28.21)	17.14 (11.43-25.36)	0.39	19.64 (11.43-25.36)	15.36 (10.36-28.22)	0.29
NO on day +7	24.64 (17.14-32.14)	16.43 (13.21-38.93)	0.35	16.43 (13.21-20.36)	24.64 (16.43-38.93)	0.16

IBMTR-SI: International Bone Marrow Transplant Registry severity index; TAS: total anti-oxidant status (mmol Trolox Eq/L); TOS: total oxidant status (μmol H2O2 Eq/L); PON1: paraoxanase-1 (U/L); TT: total thiol (μmol/L); NT: native thiol (μmol/L); DS: disulphides (μmol/L); NO: nitric oxide (μmol/L)

Table 4. Characteristics of patients according to donor type

	Haploidentical donor	Single antigen mismatched unrelated donor	Matched related donor	Matched unrelated donor	P
Age, median (minimum-maximum)	38 (26-70)	51 (31-59)	47 (23-77)	59 (49-68)	0.93
Gender, n (%)					0.70
Male	2 (66.7)	1 (33.3)	5 (71.4)	1 (50.0)	
Female	1 (33.3)	2 (66.7)	2 (28.6)	1 (50.0)	
Diagnosis, n (%)					0.63
Acute leukemia and myelodysplastic syndromes	5 (71.4)	1 (50.0)	2 (66.7)	3 (100.0)	
Other	2 (28.6)	1 (50.0)	1 (33.3)	-	
GvHD prophylaxis, n (%)					**0.02**
CNI+Mtx	-	-	4 (57.1)	-	
CNI/sirolimus+MMF	-	-	3 (42.9)	-	
PT-Cy+CNI/sirolimus+MMF	3 (100.0)	3 (100.0)	-	2 (100.0)	
Performance status, n (%)					0.32
<2	5 (71.4)	2 (100.0)	1 (33.3)	1 (33.3)	
≥2	2 (28.6)	-	2 (66.7)	2 (66.7)	
Glucksberg grade of aGvHD, n (%)					**0.009**
I or II	-	-	5 (71.4)	2 (100.0)	
III or IV	3 (100.0)	3 (100.0)	2 (28.6)	-	
IBMTR-SI of aGvHD, n (%)					0.16
A or B	1 (33.3)	1 (33.3)	6 (85.7)	2 (100.0)	
C or D	2 (66.7)	2 (66.7)	1 (14.3)	-	
Streoid response, n (%)					0.73
Non-responder	1 (33.3)	1 (33.3)	1 (14.3)	-	
Responder	2 (66.7)	2 (66.7)	6 (85.7)	2 (100.0)	

aGvHD: acute graft versus host disease; CNI: calcineurin inhibitor; Mtx: methotrexate; MMF: mycophenolate mofetil; PT-Cy: post-transplant cyclophosphamide; IBMTR-SI: International Bone Marrow Transplant Registry severity index

(NADPH) oxidase (NOX) to produce more ROS (22). ROS originating from NOX stimulates antigen presentation of dendritic cells to CD8+ T-cells (23). Toll-like receptor (TLR) mediated ROS provide maturation signals for CD4+ T-cells (24). Eventually, the disturbance of oxidative equilibrium within CD4+ T-cells may end up with hyper-inflammation and tissue necrosis (25).

The role of oxidative stress in the regulation of T-cell activation, proliferation and differentiation has been emphasized in many preclinical studies (21, 26). Nuclear factor kappa B (NF-κB), which can be activated by cytokines, activators of protein kinase C, viruses and oxidative stress, is an important pathway in T-cell activation and results in transcription of IL-2, TNF-α, interferon-γ, and their receptors (13). Thus, parameters evaluating oxidative stress seem to be attractive candidates as biomarkers, when the pivotal role of T-cells in the development of aGvHD and the high oxidative stress load generated during the process of ASCT are considered.

Endogenous NO production has been reported to exert protective effects against GvHD (27). According to previous reports, the activation of inducible nitric oxide synthase may be responsible from the increased serum NO levels observed preceding the onset of clinical GvHD (28). However, we failed to observe neither a significant change in serum NO levels during the course of aGvHD, nor any difference when compared for steroid response and grade of aGvHD.

The unfavorable effects of increased oxidative stress may be augmented in case of insufficient anti-oxidant reserves, which is evaluated by TAS, TT and NT measurements. TAS, which is an indicator of anti-oxidant activity, did not change significantly during the course of aGvHD and when compared for steroid response and grade of aGvHD. Glutathione system, also called dynamic thiol-disulphide homeostasis, constitutes the main buffer mechanism against oxidative stress. This system involves molecules with labile sulfhydryl groups, which undergo repeated reversible redox reactions catalyzed by NADPH and include glutathione, homocysteine, cysteine, cysteinylglycine and γ- glutamylcysteine (19). Glutathione may inhibit GvHD reactions via suppression of Th-17 differentiation and stimulation of T-regs (21). Although we did not observe a significant association of TT and DS during the course of aGvHD, there was a tendency for lower NT levels in the presence of higher grade of aGvHD.

PON1 is an enzyme secreted from liver. It is found mainly in the form of a stable complex together with high-density lipoprotein (HDL) and apolipoprotein A1 (ApoA1) in the circulation (21). It exerts protective effects against lipid peroxidation and stress-induced ROS formation in the endoplasmic reticulum of human endothelial cells and eliminates homocysteine-thiolactone, which is a toxic metabolite associated with the development of autoimmune, cardiovascular, neurological and malignant diseases (29). Our findings show that there is an impaired PON1 activity in steroid non-responders. This may be either a result of the complex pathophysiological interactions observed during the course of aGvHD, or may demonstrate an individual susceptibility originating from the reported interindividual variations in the enzymatic activity of PON1 isoforms (30). Due to the study design, it is not possible to evaluate whether the observed decrease in PON1 levels is the cause or result of GvHD, however, it may serve as a biomarker in both circumstances. Further studies are needed to evaluate whether there exists a causal effect. PON1, which is regarded as a potential biomarker for cellular stress, may also serve as a biomarker for aGvHD (31).

Our study is the first to explore the changes in oxidative stress parameters during the course of aGvHD. The sample size is modest, however, it may be considered big enough to have a preliminary opinion whether there exists an association between the disease and studied parameters. This research has been designed as a pilot study, and it will take some more time to recruit more patients, when the relatively low incidence of this disease in the general population is considered. Despite its limitations the prospective design and proper definition of risk groups for aGvHD allowed for important observations.

CONCLUSION

SR-aGvHD is an important cause of morbidity and mortality after ASCT. Advanced stage GI involvement and higher total grade of aGvHD is associated with steroid resistance. Lower PON1 levels may be employed as an early indicator of steroid resistance and thus may allow for the early start of more aggressive therapies. Cut-off values and possible confounders should be investigated in further studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Medicana Hospital Clinical Research Ethics Committee (Date: 24.11.2021, Decision No: BŞH-2022/39).

Informed Consent: Verbal and written informed consents were obtained from all patients before enrollment.

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. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2015; 21: 1863-9.
2. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974; 18: 295-304.
3. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol 1997; 97: 855-64.
4. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2012; 18: 1150-63.
5. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. Br J Haematol 2012; 158: 30-45.
6. Penack O, Marchetti M, Ruutu T, et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol 2020; 7: e157-e67.
7. Bacigalupo A, Milone G, Cupri A, et al. Steroid treatment of acute graft-versus-host disease grade I: a randomized trial. Haematologica 2017; 102: 2125-33.
8. Mielcarek M, Storer BE, Boeckh M, et al. Initial therapy of acute graft-versus-host disease with low-dose prednisone does not compromise patient outcomes. Blood 2009; 113: 2888-94.
9. Jagasia M, Perales MA, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. Blood 2020; 135: 1739-49.
10. Jagasia M, Greinix H, Robin M, et al. Extracorporeal photopheresis versus anticytokine therapy as a second-line treatment for steroid-refractory acute GVHD: a multicenter comparative analysis. Biol Blood Marrow Transplant 2013; 19: 1129-33.
11. Faraci M, Calevo MG, Giardino S, et al. Etanercept as Treatment of Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Patients. Biol Blood Marrow Transplant 2019; 25: 743-8.
12. Toubai T, Mathewson ND, Magenau J, Reddy P. Danger Signals and Graft-versus-host Disease: Current Understanding and Future Perspectives. Front Immunol 2016; 7: 539.
13. Colombo AA, Alessandrino EP, Bernasconi P, et al. N-acetylcysteine in the treatment of steroid-resistant acute graft-versus-host-disease: preliminary results. Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Transplantation 1999; 68: 1414-6.
14. Ali AM, DiPersio JF, Schroeder MA. The Role of Biomarkers in the Diagnosis and Risk Stratification of Acute Graft-versus-Host Disease: A Systematic Review. Biol Blood Marrow Transplant 2016; 22: 1552-64.

15. Omer AK, Weisdorf DJ, Lazaryan A, et al. Late Acute Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2016; 22: 879-83.
16. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005; 11: 945-56.
17. Kucuk A, Polat Y, Kilicarslan A, et al. Irisin Protects Against Hind Limb Ischemia Reperfusion Injury. Drug Des Devel Ther 2021; 15: 361-8.
18. Levine JE, Braun TM, Harris AC, et al. A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study. Lancet Haematol 2015; 2: e21-9.
19. Suh JH, Kanathezhath B, Shenvi S, et al. Thiol/redox metabolomic profiling implicates GSH dysregulation in early experimental graft versus host disease (GVHD). PLoS One 2014; 9: e88868.
20. Zeiser R. Advances in understanding the pathogenesis of graft-versus-host disease. Br J Haematol 2019; 187: 563-72.
21. Morris G, Gevezova M, Sarafian V, Maes M. Redox regulation of the immune response. Cell Mol Immunol 2022.
22. Forman HJ, Torres M. Redox signaling in macrophages. Mol Aspects Med 2001; 22: 189-216.
23. Mantegazza AR, Savina A, Vermeulen M, et al. NADPH oxidase controls phagosomal pH and antigen cross-presentation in human dendritic cells. Blood 2008; 112: 4712-22.
24. Gotz A, Ty MC, Rodriguez A. Oxidative Stress Enhances Dendritic Cell Responses to Plasmodium falciparum. Immunohorizons 2019; 3: 511-8.
25. Zhang B, Liu SQ, Li C, et al. MicroRNA-23a Curbs Necrosis during Early T Cell Activation by Enforcing Intracellular Reactive Oxygen Species Equilibrium. Immunity 2016; 44: 568-81.
26. Liu R, Peng L, Zhou L, Huang Z, Zhou C, Huang C. Oxidative Stress in Cancer Immunotherapy: Molecular Mechanisms and Potential Applications. Antioxidants (Basel) 2022; 11.
27. Drobyski WR, Keever CA, Hanson GA, McAuliffe T, Griffith OW. Inhibition of nitric oxide production is associated with enhanced weight loss, decreased survival, and impaired alloengraftment in mice undergoing graft-versus-host disease after bone marrow transplantation. Blood 1994; 84: 2363-73.
28. Weiss G, Schwaighofer H, Herold M, et al. Nitric oxide formation as predictive parameter for acute graft-versus-host disease after human allogeneic bone marrow transplantation. Transplantation 1995; 60: 1239-44.
29. Bacchetti T, Ferretti G, Sahebkar A. The role of paraoxonase in cancer. Semin Cancer Biol 2019; 56: 72-86.
30. Taler-Vercic A, Golicnik M, Bavec A. The Structure and Function of Paraoxonase-1 and Its Comparison to Paraoxonase-2 and -3. Molecules 2020; 25.
31. Shunmoogam N, Naidoo P, Chilton R. Paraoxonase (PON)-1: a brief overview on genetics, structure, polymorphisms and clinical relevance. Vasc Health Risk Manag 2018; 14: 137-43.

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Determination of risk factors playing a role in the transmission of COVID-19 in healthcare professionals

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ABSTRACT

Introduction: Healthcare workers and professionals have the highest risk of transmission of novel coronavirus disease-2019 (COVID-19). The risks faced by healthcare professionals can vary according to their working conditions, knowledge, attitudes and behaviours. This study aimed to identify risk factors contributing to transmission among frontline healthcare providers in the pandemic period.

Material and Method: The healthcare workers working at the school of medicine hospital and referred to the COVID-19 clinics by the filiation team following risky exposure between March 15, 2020 and December 31, 2020 were included in the study. sociodemographic features, use of protective equipment, unprotected contact data, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) Real-time reverse transcription-polymerase chain reaction (RT-PCR) test results recorded on the contact healthcare follow-up form of the participants were taken from the hospital records and analyzed retrospectively.

Results: Of the healthcare workers included in the study, 790 (58%) were female, and 571 (42%) were male, with a mean age of 33,6±8,3 years. SARS-CoV2 PCR positivity was detected in 94 (6%) participants. According to the multivariate model results, the male gender was found as a risk factor in terms of transmission which increased the risk 1.633-fold [%95 Cl; (1,048-2,544), p=0,030], working in a laboratory unit increased the risk 2.89-fold [%95 Cl; (1,322-6,316), p=0,008], and contacting out of the hospital increased the risk 7.154-fold [%95 Cl; (4,085-12,529), p <0,001], and all these were determined as independent risk factors.

Conclusion: We think that indoor units such as laboratories that do not have direct contact the patient, which seems to be risk-free in terms of transmission, contribute to the cross-contamination of COVID-19 among healthcare workers.

Keywords: COVID-19, healthcare worker, personal protective equipment, contact, risk factors

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INTRODUCTION

In the novel coronavirus disease-2019 (COVID-19) pandemic, prevention is as important as treatment itself in limiting the disease. There were significant challenges at the beginning of the pandemic, such as insufficient protective equipment, failure to provide isolation conditions, difficulty in complying with protective measures, and disruption in health care due to infected healthcare workers. Healthcare workers have been at high risk due to exposure to infection and being a source of disease due to intense patient exposure before vaccination. According to the World Health Organization (WHO), 14% of COVID-19 cases are among healthcare workers (1). It has been reported that approximately 6% of COVID-19 cases in Turkey are among healthcare workers (2). This rate is vital in controlling pandemic for the health of healthcare providers, and the maintenance of public health service. The knowledge and attitude responses of healthcare professionals about COVID-19, the precautions they take to approach the patient are as critical to the spread and control of the disease as the use of personal protective equipment (PPE) (3-6).

It is known that unprotected contact is directly related to the transmission of COVID-19 (6-8). Besides, risk factors that play role in transmission need detailed search due to the prominence of number of patients whose possible transmission source yet to be identified among infected health care providers. In addition to these, we observed that more healthcare workers were infected in some units in our hospital compared to others. Therefore, we aimed to determine different risk factors as well as known factors that play a role in transmission among healthcare workers.

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MATERIAL AND METHOD

The study was carried out with the permission of the university clinical research ethics committee (Date: 03.11.2021, Decision No: KAEK 448/2021). All study processes were conducted under the principles of the Declaration of Helsinki and ethical rules.

Study Design

The study included 1361 healthcare professionals working at the school of medicine hospital and referred to the COVID-19 clinics by the filiation team following risky exposure between March 15, 2020 and December 31, 2020. Sociodemographic data, contact risk, duration of contact, area of contact, personal protective equipment (PPE) use during contact, SARS-CoV2 PCR test results and clinical results were obtained from the contact tracking form recorded in the hospital automation system by the filiation teams. Healthcare providers who did not work in our hospital were excluded the study.

COVID-19 cases definitions were confirmed according to the definitions of the WHO (9). The confirmed cases with positive SARS-CoV2 PCR test post-exposure were considered as transmission. SARS-CoV2 viral RNA was tested using BioSpeedy COVID-19 RT-PCR (Bioeksen, Turkey) from nasopharyngeal and oropharyngeal swabs taken at admission in symptomatic participants and five or seven days after exposure from high and intermediate-risk participants.

The exposure risk of the participants was defined as low, medium and high according to the COVID-19 Filiation and contact follow-up guide of the ministry of health general directorate of public health. Healthcare workers who have come into contact with an unmasked COVID-19 patient without using PPE or a surgical mask constituted the high-risk group. Those who performed aerosol-generating procedures on a COVID-19 patient without using goggles or using a surgical mask, and healthcare workers who came into contact with a COVID-19 patient with a surgical mask without using PPE constituted the intermediate risk group. Those who came into contact with a COVID-19 patient without isolation gowns and gloves were in the low risk group. Healthcare workers caring for a COVID-19 patient using full PPE were not included in a risk group (10).

Statistical Analysis

Data were analyzed with IBM SPSS V23 (IBM SPSS, Chicago, IL, USA). Conformity to normal distribution was evaluated with the Kolmogrov-Smirnov test. The Mann-Whitney U test was used to compare the non-normally distributed age according to the groups. Chi-square and Fisher's Exact tests were used to compare categorical data according to groups. Binary logistic regression analysis was used to examine the risk factors affecting the positivity of the post-exposure SARS-CoV2 PCR result. Analysis results were presented as mean±standard deviation and median (minimum-maximum) for quantitative data, and frequency (percent) for categorical data. Significance level was taken as $p<0.05$.

RESULTS

Sociodemographic Features

A total of 1361 healthcare workers, 790 (58%) women and 571 (42%) men, were included in the study, and the mean age was 33,6±8,3 years. The healthcare workers consisted of 323 (23.7%) residents, 31 (2.3%) specialist doctors, 38 (2.8%) intern doctors, 504 (37%) nurses, 176 (12.9%) other healthcare staff, 126 (9.3%) secretaries, 114 (8.4%) healthcare technicians, 40 (2.9%) technicians providing non-health services and 9 (0.7%) security staff.

SARS-CoV2 PCR was positive in 94 (6.9%) of the participants due to exposure to patients. The ratio of male gender was significantly higher in those with positive SARS-CoV2 PCR results than those with negative results (54.3% vs 41%; p=0.012). Groups with positive and negative SARS-CoV2 PCR results were similar in terms of the mean age, presence of pregnancy, presence of comorbidity, occupational distribution, and the distribution of work units in the hospital ($p>0.05$ for each) (**Table 1**). Mortality was observed in one (1%) healthcare worker who was working as technician.

In univariate logistic regression analysis, the risk of transmission of COVID-19 was 1.704-fold higher in men (p=0.013) and 2,437-fold higher in those working in laboratory units (p=0.021). In the multivariate model analysis, being a male healthcare worker (1.633-fold; p=0.03) and working in laboratory units (2.89-fold; p=0.008) were independent risk factors for transmission (**Table 2**).

USE OF PROTECTIVE EQUIPMENT

The rate of those who did not wear surgical masks and gloves in the SARS-CoV2 positive group was significantly higher than those in the negative group (67% vs 51.9%; p=0.004 and 84% vs 71.5%; p=0.009, respectively). Positive and negative groups were similar in terms of N95 mask, goggles, face shield and isolation gowns usage rates ($p>0.05$ for each) (**Table 1**). In univariate logistic regression analysis, the healthcare workers who did not use surgical masks had a 1.887-fold higher risk of transmission than those who used, and it was found as an independent risk factor for transmission (p=0.005) (**Table 2**).

Table 1. Comparison of categorical variables according to post-exposure PCR results.

Variables	Mean±SD	Median	Min.-max.	Test statistics	p
Age				U=58028,5	0,679
Negative	33,6±8,3	32,0	18,0-63,0		
Positive	34,0±8,8	31,0	18,0-58,0		
Total	33,6±8,3	32,0	18,0-63,0		
Post-exposure COVID-19 PCR result	Negative (n=1267)	Positive (n=94)	Total (n=1361)	Test statistics	p
Gender				x^2=6,274	0,012
Female	747 (59)	43 (45,7)	790 (58)		
Male	520 (41)	51 (54,3)	571 (42)		
Pregnancy				---	1,000F
No	821 (99,5)	39 (100)	860 (99,5)		
Yes	4 (0,5)	0 (0)	4 (0,5)		
Comorbidity				---	0,251F
No	1207 (96,2)	93 (98,9)	1300 (96,4)		
Yes	48 (3,8)	1 (1,1)	49 (3,6)		
Profession				x^2=11,072	0,198
Residents	300 (23,7)	23 (24,5)	323 (23,7)		
Specialist doctor	29 (2,3)	2 (2,1)	31 (2,3)		
Nurse	481 (38)	23 (24,5)	504 (37)		
Healthcare technician	104 (8,2)	10 (10,6)	114 (8,4)		
Other healthcare staff	162 (12,8)	14 (14,9)	176 (12,9)		
Security	8 (0,6)	1 (1,1)	9 (0,7)		
Secretary	112 (8,8)	14 (14,9)	126 (9,3)		
Non-health service technician	35 (2,8)	5 (5,3)	40 (2,9)		
Intern doctor	36 (2,8)	2 (2,1)	38 (2,8)		
General Department				x^2=9,425	0,151
Clinic	801 (63,2)	58 (61,7)	859 (63,1)		
Emergency room	33 (2,6)	3 (3,2)	36 (2,6)		
Laboratory	51 (4)	9 (9,6)	60 (4,4)		
COVID-19 service	58 (4,6)	3 (3,2)	61 (4,5)		
Hospital management	79 (6,2)	7 (7,4)	86 (6,3)		
Supporting units	35 (2,8)	4 (4,3)	39 (2,9)		
ICU	210 (16,6)	10 (10,6)	220 (16,2)		
Surgical mask				x^2=8,079	0,004
No	657 (51,9)	63 (67)	720 (52,9)		
Yes	610 (48,1)	31 (33)	641 (47,1)		
N95 mask				x^2=1,086	0,297
No	1144 (90,4)	88 (93,6)	1232 (90,6)		
Yes	122 (9,6)	6 (6,4)	128 (9,4)		
Protective glasses				x^2=3,773	0,052
No	1133 (89,5)	90 (95,7)	1223 (89,9)		
Yes	133 (10,5)	4 (4,3)	137 (10,1)		
Face shield				x^2=0,775	0,379
No	1167 (92,2)	89 (94,7)	1256 (92,4)		
Yes	99 (7,8)	5 (5,3)	104 (7,6)		
Protective gown				x^2=1,826	0,177
No	1019 (80,5)	81 (86,2)	1100 (80,9)		
Yes	247 (19,5)	13 (13,8)	260 (19,1)		
Gloves				x^2=6,844	0,009
No	905 (71,5)	79 (84)	984 (72,4)		
Yes	360 (28,5)	15 (16)	375 (27,6)		

Table 1. Comparison of categorical variables according to post-exposure PCR results (continued)					
Post-exposure COVID-19 PCR result	**Negative (n=1267)**	**Positive (n=94)**	**Total (n=1361)**	**Test istatistics**	**p**
Contact duration					
<15 minutes	353 (27,9)	13 (13,8)	366 (26,9)	x^2=8,763	0,003
≥15 minutes	914 (72,1)	81 (86,2)	995 (73,1)		
Contact risk					
High	456 (36)a	69 (73,4)b	525 (38,6)	x^2=56,502	<0,001
Intermediate	523 (41,3)a	24 (25,5)b	547 (40,2)		
Low	278 (21,9)a	1 (1,1)b	279 (20,5)		
Non-applicable	10 (0,8)	0 (0)	10 (0,7)		
Contact area					
Hospital	1204 (95)	69 (73,4)	1273 (93,5)	x^2=67,655	<0,001
Out of the hospital	63 (5)	25 (26,6)	88 (6,5)		
Contact area: hospital					
Working	706 (58,6)	46 (66,7)	752 (59,1)	x^2=1,740	0,187
Social	498 (41,4)	23 (33,3)	521 (40,9)		
Patient contact					
Aerosol-forming procedures	36 (12,6)	0 (0)	36 (12)	---	0,389F
Nonaerosol-forming procedures	250 (87,4)	14 (100)	264 (88)		
Contact area: out of the hospital					
Home	34 (54)	20 (80)	54 (61,4)	x^2=5,465	0,065
Hospital service vehicle	3 (4,8)	0 (0)	3 (3,4)		
Restaurant, public transport	26 (41,3)	5 (20)	31 (35,2)		

Table 2. Examination of the risk factors affecting the positivity of post-exposure PCR results.				
	Univariate		**Multivariate***	
	OR (%95 CI)	**p**	**OR (%95 CI)**	**p**
Age	1,005 (0,98-1,031)	0,683		
Gender (male)	1,704 (1,118-2,596)	0,013	1,633 (1,048-2,544)	0,030
Comorbidity (Yes)	0,27 (0,037-1,981)	0,198		
Profession	1,077 (0,988-1,174)	0,092		
General Department (Clinics)				
Emergency room	1,255 (0,374-4,217)	0,713	1,445 (0,423-4,935)	0,557
Laboratory	2,437 (1,143-5,196)	0,021	2,89 (1,322-6,316)	0,008
COVID-19	0,714 (0,217-2,35)	0,580	0,662 (0,193-2,271)	0,511
Hospital management	1,224 (0,54-2,772)	0,628	1,303 (0,564-3,01)	0,536
Supporting units	1,578 (0,542-4,593)	0,402	0,75 (0,237-2,372)	0,624
ICU	0,658 (0,33-1,309)	0,233	0,529 (0,257-1,088)	0,083
Surgical mask (no)	1,887 (1,211-2,941)	0,005		
N95 (no)	0,639 (0,274-1,493)	0,301		
Protective glasses / face shield (no)	0,456 (0,182-1,141)	0,093		
Protective uniform (no)	0,662 (0,363-1,209)	0,179		
Gloves (no)	2,096 (1,19-3,69)	0,010		
Contact duration (<15 minutes)	2,406 (1,323-4,377)	0,004	1,762 (0,949-3,273)	0,073
Contact risk				
High	42,066 (5,809-304,593)	<0,001		
Intermediate	12,757 (1,717-94,799)	0,013		
Contact area (out of hospital)	6,924 (4,104-11,682)	<0,001	7,154 (4,085-12,529)	<0,001
Contact area: hospital (working)	0,709 (0,424-1,185)	0,189		
Contact area: out of hospital (home)	3,058 (1,013-9,259)	0,047		

Contact

In group with positive SARS-CoV2 PCR, the rate of those with a contact duration of 15 minutes or longer, high-risk contacts, out-of-hospital contact were significantly higher than the negative group (86.2% vs 72.1%; p=0.003 and 73.4% vs 36%; p<0.001 and 73.4% vs 95%; p<0.001 respectively) (**Table 1**).

There was no significant difference in transmission between the working and the social areas in the hospital, as well as among home, hospital service vehicle, restaurant and public transportation outside the hospital. In addition, no difference was noted between the procedures of aerosol-forming and not-forming. (p>0.05 for each) (**Table 1**).

In univariate logistic regression analysis, the risk of transmission was 2,406-fold higher in those with a contact duration of 15 minutes or longer (p=0.004). The risk was 42,066-fold higher in those with high-contact risk (p<0.001), and it was 6,924-fold higher in those whose contact area was out of hospital (p<0.001). The risk was 3.058-fold higher in those whose contact area was home (p=0.047). In the multivariate model analysis, those with contact area was out of the hospital had a 7,154-fold higher risk of transmission, and this was an independent risk factor (p<0.001) (**Table 2**).

We observed that the number of contacts increased as the pandemic prolonged (**Figure 1**). In addition, in daily analysis, we found that it decreased towards the weekend (**Figure 2**).

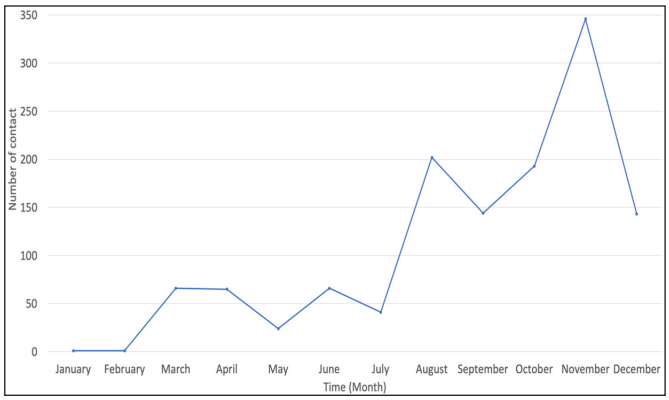

Figure 1. The number of risky contacts in 2020.

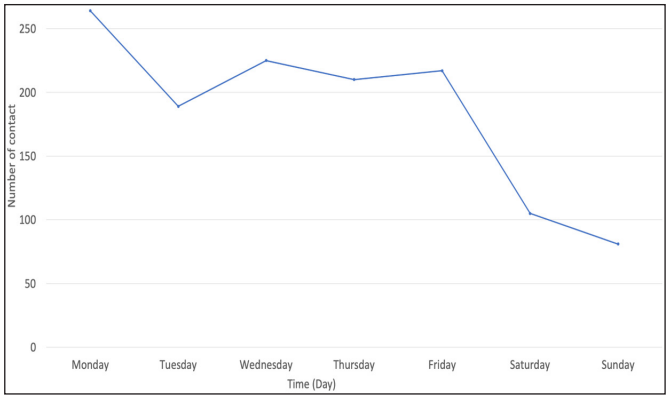

Figure 2. The number of risky contacts on daily.

DISCUSSION

The healthcare professionals' knowledge, attitudes, and behaviours about COVID-19 can affect patient management and pandemic control. The deficiencies of the healthcare workers in taking precautions against COVID-19 may make pandemic control more difficult (5, 11, 12).

While some studies reported no relationship between the transmission of COVID-19 and gender (13, 14). Another study reported that male gender was an independent risk factor for transmission (15). Authors explained the higher incidence of disease in males by behavioural factors such as low handwashing rates and non-compliance with rules (16, 17). In this study, the ratio of male gender was significantly higher in those with positive group than those with negative group (54.3% vs 41%; p=0.012). We found that male gender was an independent risk factor for transmission. The risk of transmission of COVID-19 was 1.704-fold higher in men (p=0.013). Since we obtained the participants' data mainly from declarations, we were not able to evaluate handwashing compliance adequately. The risk of transmission can be reduced by close observation following education of male healthcare workers who have high risk.

The use of face protection equipment is of great importance in preventing transmission (6-8). Exposure to the aerosols of infected patients without protective equipment has increased the risk of transmission (6,18). Lammers et al. (19) recommend taking precautions against airborne transmission, especially during the aerosol-generating processes. Bartoszko et al. (20) reported that the use of high-quality surgical masks could be as reliable as N95 masks in healthcare workers. The groups in our study were similar in terms of aerosol-generating procedures rates. This may be due to undetailed recording and explanations of procedures by healthcare providers and may suggest that a surgical mask may be sufficient in aerosol-generating procedures.

Other studies reported that the transmission of COVID-19 was significantly higher in healthcare workers who do not use PPE and led to increase in risk 3.8-5.9-fold (14, 21). It has thus shown that many healthcare workers were protected from transmission by using PPE before the vaccine (6). We found that the risk for contagion was 1.887-fold higher in those who did not use a surgical mask but not wearing an N95 mask did not increase the risk (p=0,005). We think surgical masks could be as reliable as N95 masks in healthcare workers. Bartoszko et al. (20) support this. We determined that not wearing gloves was a risk factor; the risk was 2,096-fold higher in participants without gloves but not using equipment such as face shields and safety glasses did not increase the risk (p=0.010). A contaminated environment is one of the major risk factors for healthcare-associated infections, The risk of transmission is high even when touching the mouth, nose, eyes and face skin through hands. Some studies have suggested that viral inoculum of SARS-CoV-2 could be transmission of disease (18). Our findings support that there is more virus inoculum with hand contact. The findings of our study show that healthcare workers who do not use surgical masks or gloves have a much more significant risk of transmission than those who do not use other PPE. Groups were similar in terms of other PPE use ratios.

Only one out of 94 healthcare workers in our hospital died of COVID-19. SARS-CoV2 can also be transmitted through the air, indoor and this contributes to the persistence of SARS-CoV2 in crowded areas (22,23). We found that the working area distributions between the positive and negative groups were similar. However, healthcare providers working in laboratory units had a 2,437-fold higher risk of transmission. These findings may explain why there is more transmission among healthcare workers in these areas. These units pose a risk for susceptible healthcare workers. We think that indoor units such as laboratories that direct patient contact considered unexpected which seems to be risk-free in terms of transmission, contribute to the cross-contamination of COVID-19 among healthcare workers.

Celebi et al. (24) reported that being in contact without a mask for 15 minutes or longer in the same room during the staff break increases the risk of transmission 7.42-fold. In the positive group, the risk rate of those with a contact duration of 15 minutes or longer was significantly higher than the negative group (86.2% vs 72.1%). We found that longer contact duration increased the risk of transmission by 2,406-fold. Another study showed that high-risk contact increased the risk of transmission 1.7 (25). The rate of high-risk contact in the positive group was significantly higher than that in the negative group (73.4% vs 36%). We showed that high-risk contact had 42,066-fold higher risk. These findings show that healthcare workers have an expected increased risk of transmission if they have high-risk contact.

Some studies have shown that the rate of household or community-acquired COVID-19 transmission is higher than that of hospital-acquired transmission (15, 26). In the positive group, the rate of those with out-of-hospital contact was significantly higher than the negative group (95% vs 73.4%). In this study, contact outside the hospital was found as an independent risk factor that caused the transmission 7,154-fold higher than in-hospital contact. In addition, if the contact was at home, the risk of transmission was 3,058-fold higher. These results showed that especially household contact played a role in increasing the transmission of COVID-19 in healthcare workers. Therefore, it is essential to comply with protective contact measures at home as in the hospital.

Galán et al. (13) reported that the risk of transmission in healthcare workers working in the COVID-19 unit was 1.7-fold higher. Madran et al. (14) reported that it was 2.7-fold higher. Celebi et al. (24) reported the infection rate as 8.3% in the COVID-19 unit, while it was 3.4% in other units. Working in the COVID-19 unit was not found as a risk factor for the transmission in our study. This can be explained by the careful compliance of the staff to the protective contact precautions in these units.

Some studies revealed that doctors or nurses had a higher risk of the transmission of COVID-19 (13, 27). However, Erol et al. (15) revealed that healthcare workers other than doctors had a higher risk. We found no significant relationship between the transmission of COVID-19 and the profession. More detailed and extensive studies are needed to clarify this situation.

We observed that the number of contacts increased as the pandemic prolonged. This may be due to increasing number of patients. Furthermore, the observation that decrease towards the end of the week may be due to decrease in the workload towards that time period, and fewer healthcare workers working at the weekend. Workload may cause a decrease in compliance with infection control measures. Healthcare workers should be trained on this subject frequently.

The participant data obtained without any objective evaluation may include the limitations of our study. Provided data were created by health workers' responses. However, the number of participants was kept high in order to reduce the margin of error. In addition, due to the mutations, the contagiousness of the disease has increased gradually. Therefore, the results of our study, which included patients in 2020, may not fully reflect current risk factors for contagion.

CONCLUSION

In addition to the known risk factors that play a role in the transmission to healthcare workers, we would like to draw attention to the indoor areas in which direct patient contact considered unexpected in the hospital. These areas, which seem risk-free in terms of transmission, are at high risk and contribute to the cross-contamination of COVID-19 among healthcare workers. We want to emphasize again that we must comply with infection control measures at indoor hospital areas that direct patient contact seemed unexpected.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of the Ondokuz Mayıs University Clinical Research Ethics Committee (Date: 03.11.2021, Decision No: KAEK 448/2021).

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. Prevention, identification and management of health worker infection in the context of COVID-19 [Internet]. World Health Organization. [cited 2020 Oct 30]. Available from: https://www.who.int/publications/i/item/10665-336265
2. COVID-19 Pandemisi İki Aylık Değerlendirme Raporu [Internet]. Türk Tabipler Birliği COVID-19 Danışma ve İzleme Kurulu. [cited 2020 Aug 19]. Available from: https://www.ttb.org.tr/userfiles/files/covid19-rapor.pdf
3. Gómez-Ochoa SA, Franco OH, Rojas LZ, et al. COVID-19 in health-care workers: a living systematic review and meta-analysis of prevalence, risk factors, clinical characteristics, and outcomes. Am J Epidemiol 2021; 190: 161-75.
4. Shreffler J, Petrey J, Huecker M. The Impact of COVID-19 on Healthcare Worker Wellness: A Scoping Review. West J Emerg Med 2020; 21: 1059-66.
5. Sahu AK, Amrithanand V, Mathew R, Aggarwal P, Nayer J, Bhoi S. COVID-19 in health care workers-A systematic review and meta-analysis. Am J Emerg Med 2020; 38: 1727-31.
6. Gholami M, Fawad I, Shadan S, et al. COVID-19 and healthcare workers: A systematic review and meta-analysis. Int J Infect Dis 2021; 104: 335-46.
7. Ha JF. The COVID-19 pandemic, personal protective equipment and respirator: A narrative review. Int J Clin Pract 2020; 74: e13578.
8. Li DT, Samaranayake LP, Leung YY, Neelakantan P. Facial protection in the era of COVID-19: A narrative review. Oral Dis 2021; 27: 665-73.
9. WHO COVID-19 Case definition [Internet]. World Health Organization. [cited 2020 Aug 8]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV Surveillance_Case_Definition-2020.1
10. Temaslı Takibi, Salgın Yönetimi, Evde Hasta İzlemi ve Filyasyon [Internet]. T.C. Sağlık Bakanlığı COVID-19 Bilgilendirme Platformu. [cited 2020 Mar 11]. Available from: https://covid19.saglik.gov.tr/TR-66339/temasli-takibi-salgin-yonetimi-evde-hasta-izlemi-ve-filyasyon.html
11. Wei JT, Liu ZD, Fan ZW, Zhao L, Cao WC. Epidemiology of and risk factors for COVID-19 infection among health care workers: a multi-centre comparative study. Int J Environ Res Public Health 2020; 17: 7149.
12. Zheng C, Hafezi-Bakhtiari N, Cooper V, et al. Characteristics and transmission dynamics of COVID-19 in healthcare workers at a London teaching hospital. J Hosp Infect 2020; 106: 325-9.
13. Galán MI, Velasco M, Casas ML, et al. Hospital-Wide SARS-CoV-2 seroprevalence in health care workers in a Spanish teaching hospital. Enferm Infecc Microbiol Clin 2020; 40: 302-309.
14. Madran B, Keske S, Beşli Y, Bozkurt İ, Ergönül Ö. The risk of SARS-CoV-2 infection among healthcare workers. Infect Dis Clin Microbiol 2020; 2: 54-60.
15. Erol Ç, Yanık-Yalçın T, Sarı N, Azap Ö, Arslan H. Predictors of COVID-19 among Healthcare Workers who were Exposed to COVID-19. Infect Dis Clin Microbiol 2021; 3: 87-96.
16. Acharya Y, Pant S, Gyanwali P, et al. Gender disaggregation in COVID-19 and increased male susceptibility. J Nepal Health Res Counc 2020; 18: 345-50.
17. Bwire GM. Coronavirus: Why Men are More Vulnerable to Covid-19 Than Women? SN Compr Clin Med 2020: 1-3.
18. Kim H, Hegde S, LaFiura C, et al. Access to personal protective equipment in exposed healthcare workers and COVID-19 illness, severity, symptoms and duration: a population-based case-control study in six countries. BMJ Global Health 2021; 6: e004611.
19. Lammers MJ, Lea J, Westerberg BD. Guidance for otolaryngology health care workers performing aerosol generating medical procedures during the COVID-19 pandemic. J Otolaryngol Head Neck Surg 2020; 49: 1-8.
20. Bartoszko JJ, Farooqi MAM, Alhazzani W, Loeb M. Medical masks vs N95 respirators for preventing COVID-19 in healthcare workers: A systematic review and meta-analysis of randomized trials. Influenza Other Respir Viruses 2020; 14: 365-73.
21. Contejean A, Leporrier J, Canouï E, et al. Transmission routes of severe acute respiratory syndrome coronavirus 2 among healthcare workers of a French university hospital in Paris, France. Open Forum Infect Dis 2021; 8: ofab054.
22. Centers for Disease Control and Prevention (CDC). Last accessed date: 2021 August 20. Available from: https://www.cdc.gov/infectioncontrol/pdf/guidelines/environmental-guidelines-P.pdf
23. Azuma K, Yanagi U, Kagi N, Kim H, Ogata M, Hayashi M. Environmental factors involved in SARS-CoV-2 transmission: effect and role of indoor environmental quality in the strategy for COVID-19 infection control. Environ Health Prev Med 2020; 25: 1-16.
24. Çelebi G, Pişkin N, Bekleviç AÇ, et al. Specific risk factors for SARS-CoV-2 transmission among health care workers in a university hospital. Am J Infect Control 2020; 48: 1225-30.
25. Varona JF, Madurga R, Peñalver F, et al. Seroprevalence of SARS-CoV-2 antibodies in over 6000 healthcare workers in Spain. Int J Epidemiol 2021; 50: 400-9.
26. Canova V, Lederer Schläpfer H, Piso RJ, et al. Transmission risk of SARS-CoV-2 to healthcare workers-observational results of a primary care hospital contact tracing. Swiss Med Wkly 2020; 150: w20257
27. Bandyopadhyay S, Baticulon RE, Kadhum M, et al. Infection and mortality of healthcare workers worldwide from COVID-19: a systematic review. BMJ Glob Health 2020; 5: e003097.

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Postlaminectomy instability–is fusion essential in degenerative lumbar stenosis surgery?

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ABSTRACT

Aim: To examine the incidence of postlaminectomy instability in cases of lumbar spinal stenosis who underwent facet-preserving laminectomy and decompression with the classical laminectomy technique, together with comorbid diseases, and to determine whether fusion is needed.

Material and Method: The patients who were operated by the same surgeon in the same hospital between 2017 and 2019 and followed up in terms of instability in the postoperative 1st and 6th months were evaluated retrospectively with their clinical findings, comorbid diseases and radiological images. White and Panjabi's instability criteria were used. It was analyzed with SPSS 23.00 statistical package program. Data were analyzed by descriptive statistics (number, percentage distribution, mean and standard deviation), t-test and ANOVA.

Results: A total of 53 patients, 22 male (41.5%) and 31 female (58.5%) were included in the study. Age, surgical precedures and comorbid diseases were investigated. None of the patients, but 2 patients with osteoporosis with or without diabets, had postlaminectomy instability.

Conclusion: It has been shown in our study that decompressive and facet-preserving surgery performed at 2 levels or less using only the classical laminectomy technique does not cause instability in patients without osteoporosis alone or with diabetes, especially in the first 6 months, and can be safely applied to patients. Osteoporosis alone or in association with diabetes mellitus suggests increased postoperative instability.

Keywords: Decompression, laminectomy, spinal stenosis

INTRODUCTION

Degenerative lumbar stenosis is the most common disease in the aging spine. Surgical decompression is effective and important in the treatment of neurogenic claudication, but the effect and necessity of fusion surgeries are not as clear as decompression surgeries in the literature. Postlaminectomy instabilities are a common reason for reoperation after decompression procedures. Posterior transpedicular stabilization and fusion surgery to be performed in addition to laminectomy reduces the risk of instability, but increases the duration of surgery, increases morbidity and mortality rates, increases the rates of interventional complications, may cause adjacent segment disease in the long term, and increases the financial burden of health services. In the literature, in which cases fusion is necessary and in which cases it is not, different results are published in different series.

The aim of this study is to retrospectively examine the incidence of postlaminectomy instability in cases of lumbar spinal stenosis who did not have preoperative instability, who underwent facet-preserving laminectomy and decompression with the classical laminectomy technique, considering comorbid diseases, and to evaluate whether fusion is required in addition to laminectomy in these patients.

MATERIAL AND METHOD

The study was conducted with the permission of the Muğla Sıtkı Koçman University Clinical Researches Ethics Committee (Date: 08/08/2019, Decision No: 09/V). All procedures were carried out in accordance with the ethical rules and the principles of the declaration of Helsinki.

The patients who were operated by the same surgeon in the same hospital between 2017 and 2019 and followed up in terms of instability in the postoperative 1st and 6th months were retrospectively analyzed with clinical findings and radiological images.

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Laminectomies up to 2 levels, flavectomy and foraminotomies were performed in these patients who were operated in the prone position under intratracheal general anesthesia with the classical laminectomy technique. Patients with instability on preoperative dynamic radiographs, those who underwent more than bilateral 1/3 medial facetectomy, those who underwent surgery in 3 or more level functional vertebral segments, patients who did not have at least 6 months of follow-up, and patients without demographic data and radiological imaging were excluded from the study. Orthoses or corsets were not used in any of the patients in the postoperative period in order to preserve functional movement. Radiological instability was evaluated according to Panjabi and White's instability criteria, by comparison with preoperative and postoperative (1st and 6th months) 2-way lumbosacral radiographs (neutral AP and neutral lateral) and functional lumbosacral vertebral radiographs (lateral hyperflexion and lateral hyperextension). More than 5 millimeters of translation and/or more than 15 degrees of angulation in a functional segment was considered as radiological instability and postlaminectomy instability.

Statistical Analysis

All records and data of the patients were analyzed with SPSS 23.00 statistical package program. Data were analyzed by descriptive statistics (number, percentage distribution, mean and standard deviation), t-test and ANOVA. Parameters that were determined not to show normal distribution were compared using the Mann-Whitney U test. The findings were evaluated at 95% confidence interval and 5% significance level.

RESULTS

A total of 53 patients, 22 male (41.5%) and 31 female (58.5%) were included in the study. In both sexes, the mean age was 61.1887 ± 11.14081 (41-86), and the median age was 68. The mean duration of the surgical procedure was 60.47 minutes (44 – 96 minutes). It was seen that 25 patients had 1 level (47.2%) and 28 patients had 2 level (52.8%) total laminectomy. Surgical site infection was not observed in any patient. When the comorbid diseases of the patients are examined; 21 (39.6%) patients had no additional disease, 12 (22.6%) patients had only hypertension, 8 (15.1%) patients had hypertension and diabetes, 4 (7.5%) patients had only diabetes, 3 (5,7%) patients had diabetes and osteoporosis, 2 (3.8%) patients had only coronary artery disease, 2 (3.8%) patients had coronary artery disease and diabetes, and 1 (1.9%) patient had only osteoporosis (**Table 1, 2, 3**).

Table 1. Demographic data

Sex	n	%
Male	22	41.5
Female	31	58.5
Total	53	100.0

Table 2. Patient age, operation time and number of laminectomy level(s)

	Patient Age (years)	Operation Time (min)	Number of Laminectomy Level(s)
Average	65.1887	60.4717	1.5283
Median	68.0000	68.0000	2.0000
Standard deviation	11.14081	21.53673	0.50398
Min	41.00	44.00	1.00
Max	86.00	96.00	2.00

Table 3. Comorbid disease(s)

Comorbid disease(s)	n	%
No	21	39.6
Diabetes	4	7.5
Hypertension	12	22.6
Coronary artery disease	2	3.8
Hypertension and diabetes	8	15.1
Osteoporosis	1	1.9
Diabetes and osteoporosis	3	5.7
Coronary artery disease and diabetes	2	3.8
Total	53	100.0

Panjabi and White's radiological instability criteria were used in the evaluation of instability by AP, lateral, hyperflexion and hyperextension radiographs in the 1st and 6th months postoperatively. More than 5 millimeters of translation and more than 15 degrees of angulation in a vertebral functional segment were considered as radiological instability and postlaminectomy instability. Accordingly, no radiological instability was observed in the postoperative 1st month. In the 6th month postoperatively, instability was detected in 3 patients (**Table 4**).

Table 4. Comparison of presence of postoperative instability with parameters

	Postoperative 6th month instability presence		
	Yes (n:3)	No (n:51)	P value
Gender (%)			0.258
Male	-	23/51 (%44)	
Female	3/3 (100%)	28/51 (%56)	
Age (average)	71,33±6,50	65.14±11,06	0.888
Additional disease (%)	100 %	58 %	0.001*
Number of laminectomy level(s) (%)			0.173
1 level	-	25/51 (50%)	
2 levels	3/3 (100%)	25/51 (50%)	
Follow-up time / month (average)	26±12,4	20±21,99	0.374

* $p < 0.05$

There was no statistically significant difference between gender, age, laminectomy level(s), duration, and instability development at the postoperative 6th month (z=-1.203, -0.140, -1.349, -0.888, respectively; p=0.229, 0.888, 0.177, 0.374) according to the Mann-Whitney U test. When the relationship between the presence of comorbidity and the development of instability at the postoperative 6th month was examined, a statistically significant difference was found (p=0.017, z=-2.236, U=5.0) (**Figure**).

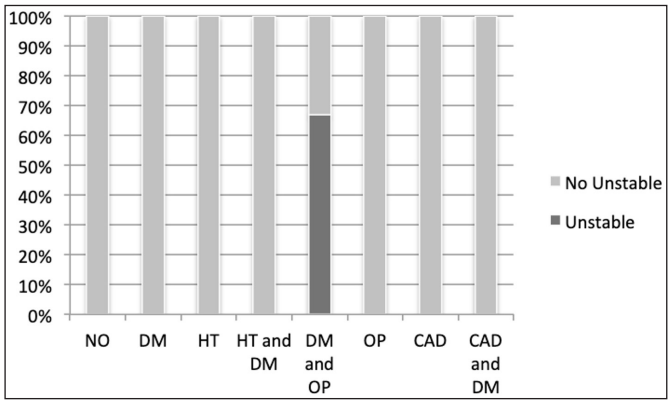

Figure. Comorbid diseases and instability rates
DM: diabetes mellitus, HT: hypertension, OP: osteoporosis, CAD: coronary artery disease

Logistic regression testing was performed to determine the effects of age, gender, operative level(s), postoperative duration, and comorbidities on patients' probability of postoperative instability. Hosmer-Lemeshow goodness-of-fit statistical test p values were found to be >0.05 (H-L statistics=6.82, p=0.559). In the logistic regression model, postoperative instability variance was 47% (Nagelkerke R2) and adjusted classification was 94.3%. Osteoporosis alone or in association with diabetes mellitus was associated with increased postoperative instability (respectively; RR: 1.59, 95% CI: 1.31-3.98, p-value: 0.047, and RR: 1.90, 95% CI: 1.54-12.10, p-value: 0.003).

DISCUSSION

It has been shown in our study that decompressive and facet-preserving surgery performed at a distance of 2 levels or less, using only the classical laminectomy technique, did not cause instability in patients without osteoporosis or diabetes and osteoporosis coexistence, especially in the first 6 months.

Symptomatic lumbar spinal stenosis leads to progressive neurogenic claudication, radicular pain and loss of strength. Surgical interventions may be required to relieve pain, eliminate limitation of movement, and improve quality of life. Variable degrees of disc herniations, hypertrophies and cyst formations in the zygoapophyseal facet joints, and hypertrophy of the ligamentum flavum play a role in the pathoanatomical causes of this disease. Neural stenoses that cause central canal stenosis cause neurogenic claudication, and stenoses that occur in lateral recession cause radiculopathies. Surgical indication is mainly due to neurological deficits or unresponsiveness to conservative treatments.

Instability is defined as the loss of the ability of the spine not to damage and irritate the spinal cord under physiological loads, in addition to deformity and structural changes, and loss of mobility (1). White and Panjabi (2) described that sagittal plane translation 4.5 mm on flexion-extension radiographs or translation between two vertebral bodies greater than 15% of the vertebral body, or sagittal plane rotation greater than 15° at L1-L2, L2/L3 or L3/L4 levels determined that it is more than 20°, at the L4/L5 level and more than 25°, and at the L5/S1 level as radiological instability criteria.

Among decompressive techniques, laminectomy is considered as the gold standard surgical treatment. Although the short-term results and benefits of laminectomy in lumbar spinal stenosis have been studied in detail, the concerns about iatrogenic instability and the appropriate indications for concomitant fusion have been ongoing for a long time (3).

Basically, fusion surgeries are recommended in cases of degenerative spondylolisthesis or dynamic instability (4). Laminectomy and facetectomy performed in decompression surgery can lead to overt and iatrogenic instability. Postlaminectomy instabilities are a common reason for reoperation after decompression procedures. This risk is minimized in minimally invasive techniques and facet preserving interventions. In our study, cases without preoperative instability were included, and the effect of facet-sparing surgeries on comorbid diseases was examined. In terms of postlaminectomy instability, lower rates were obtained than in the literature.

Post-laminectomy deformity is the clinical and radiological expression of loss of resistance of the posterior elements to traction forces, whether or not associated with insufficient capacity to support the anterior portion of the spinal column. Occasionally, it may result in progressive deformity accompanied by neurological deficit due to compression of the nerve tissues within the spinal canal. Deformities after laminectomy are seen relatively early. It has been stated that postoperative immobilization will not prevent the appearance of deformity, but may delay the deformity (5).

Although the facet joints are often preserved during laminectomy, the lamina, interspinous, supraspinous, and flavum ligaments are cut and/or removed. All of these structures have stabilizing functions for the spinal motion segment. Removal of these structures can lead to clinical spinal instability, defined as an increase in range of motion

(ROM), spinal stiffness leading to reduced physiological conditions, and/or neurological disturbances through reduction in ultimate spinal strength and nerve root compression, deformation such as scoliosis or spondylolisthesis, and/or pain (2). Currently, there are no strict rules about when additional instrumentation should be added (6,7). The biomechanical effects of a single-level lumbar laminectomy and additional instrumentation and adjacent segment effects are not yet known precisely (8,9). After laminectomy, it is possible that the rotational stability will decrease with the weakening of the posterior elements, which are soft and bony tissues, which are responsible for axial rotation (10-12). Although torsional forces have been studied in untreated lumbar spines, studies related to torsional biomechanics of laminectomy are limited (13, 14).

It has been reported that, as an alternative to laminectomy, bilateral laminotomy provides adequate and safe decompression of the spinal canal in patients with lumbar stenosis, improves the quality of life by reducing the symptoms of the patients, has similar neurological outcomes, a lower incidence of complications and complications, and a similar iatrogenic instability rate (15).

In our study, facet preserving classical laminectomy to be performed up to 2 levels for patients with osteoporosis or without diabetes and osteoporosis; It has been shown that it can be safely applied to patients, considering it reduces symptoms, provides neural decompression, and the risk of developing iatrogenic instability. Examination of laminectomy performed in more segments and longer follow-up period can be considered as limitations of the study.

CONCLUSION

In conclusion, there is literature information supporting both techniques in terms of classical laminectomy or classical laminectomy combined with fusion surgery. It is obvious that it will be more appropriate to determine a patient-specific surgical treatment by combining the appropriate patient, the appropriate indication and the appropriate surgical technique, and the treatment modalities will be re-examined as biomechanical studies increase and spine biomechanics are better understood.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of the Muğla Sıtkı Koçman University Clinical Research Ethics Committee (Date: 08/08/2019, Decision No: 09/V).

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. White AA, 3rd, Johnson RM, Panjabi MM, Southwick WO. Biomechanical analysis of clinical stability in the cervical spine. Clin Orthop Relat Res 1975; 109: 85–96.
2. White AA, Panjabi MM. Clinical biomechanics of the spine. 2. Philadelphia: Lippincott; 1990. pp. 23–45.
3. Mosenthal WP, Dickherber JL, Saitta BH, Lee MJ. Post laminectomy instability. Semin Spine Surg 2019; 31: 100713.
4. Resnick DK, Watters WC III, Sharan A, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 9: lumbar fusion for stenosis with spondylolisthesis. J Neurosurg Spine 2014; 21: 54–61.
5. Lutz FS, Munhoz da Rocha LS. Post-Laminectomy Deformities. Coluna/Columna 2014; 13: 279-81.
6. Fox MW, Onofrio BM. Indications for fusion following decompression for lumbar spinal stenosis. Neurosurg Focus 1997; 3: e2.
7. Herkowitz HN, Kurz LT. Degenerative lumbar spondylolisthesis with spinal stenosis. A prospective study comparing decompression with decompression and intertransverse process arthrodesis. J Bone Joint Surg Am 1991; 73: 802-8.
8. Radcliff KE, Kepler CK, Jakoi A, et al. Adjacent segment disease in the lumbar spine following different treatment interventions. Spine J 2012; 13: 1339-49.
9. Reeves NP, Narendra KS, Cholewicki J. Spine stability: the six blind men and the elephant. Clin Biomech 2008; 22: 266-74.
10. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine 2006; 31: 2151- 61.
11. Farfan HF, Cossette JW, Robertson GH, Wells RV, Kraus H. The effects of torsion on the lumbar intervertebral joints: the role of torsion in the production of disc degeneration. J Bone Joint Surg Am 1970; 52: 468-97.
12. Gordon SJ, Yang KH, Mayer PJ, Mace AH, Jr, Kish VL, Radin EL. Mechanism of disc rupture. A preliminary report. Spine 1991; 16: 450-6.
13. Adams MA, Hutton WC. The relevance of torsion to the mechanical derangement of the lumbar spine. Spine 1881; 6: 241-8.
14. Farfan HF. Effects of torsion on the intervertebral joints. Can J Surg 1969; 12: 336-41.
15. Pietrantonio A, Trungu S, Famà I, Forcato S, Miscusi M, Raco A. Long-term clinical outcomes after bilateral laminotomy or total laminectomy for lumbar spinal stenosis: a single-institution experience. Neurosurg Focus 2019; 46: E2.

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Local control results in extremity soft tissue sarcomas

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ABSTRACT

Aim: The aim of this study is to investigate local control results and effective predictive factors in local control of extremity soft tissue sarcomas, retrospectively.

Material and Method: 51 patients underwent postoperative adjuvant radiotherapy (RT) in Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between October 2008-January 2022. Patients who underwent post-operative adjuvant RT were treated with 60-68 Gy in 2 phases from 2 Gy /day using conformal radiotherapy technique. IMA chemotherapy protocol was applied to 31.4% of the patients after radiotherapy.

Results: The median follow up time was 46 months range (1-135). Recurrence was detected in 5 of the patients and the mean time of recurrence was 11.6 months (min: 3-max: 27). 10 patients developed metastasis at follow-up, the mean time until metastasis was 27 months (min: 18- max: 46). The mean overall survival (OS) was 103 (min:4-max:139) months and the OS of 2, 5 and 10 years were 93%, 65% and 60%, respectively. Disease-free survival (DFS) was 97 (min:4-max:139) months; 2, 5 and 10 years of DFS were 77%, 65% and 60%, respectively. The OS in patients aged ≥65 years old was significantly lower than in patients <65 years old (p=0.02). Overall and disease-free survival was significantly lower in patients undergoing chemotherapy (p=0.037 for overall survival, p=0.013 for disease-free survival). The occurrence of recurrence, metastasis or death within 3 years after the operation was significantly higher than after 3 years (p<0.001). Local failure was significantly higher in grade 3 tumors (p=0.05). All patients who recurred had grade 3 tumors. Metastasis and excitus were significantly higher in the follow-up of patients who underwent chemotherapy at one point during their treatment (p=0.027 for metastasis, p=0.042).

Conclusion: While favorable local control results are obtained with adjuvant high dose-conformal radiotherapy in extremity sarcomas, close follow up is important for distant metastasis and local recurrence, especially in the first 3 years.

Keyword: Extremity, sarcoma, survival, age, grade, radiotherapy

INTRODUCTION

Soft tissue sarcomas are tumors of mesenchymal origin and originate from the extremities in 43% of cases (1). The main treatment of these tumors is surgery and radiotherapy (RT) can be applied preoperatively or postoperatively. With the addition of radiotherapy to limb-sparing surgery, local control results are equivalent to amputation in soft tissue sarcomas (2). Surgical margin safety is the most important predictive factor in local recurrence in surgical treatment (3-6).

The standard surgical approach in extremity soft tissue sarcomas is wide local excision with a negative surgical margin (R0). In marginal excision, the tumor tissue is removed together with the reactive zone called pseudo-capsule. While in R1 resection, microscopic tumor tissue remains; in R2 resection macroscopic residual tumor remains. According to the NCCN (National Comprehensive Cancer Network) guidelines, 10 mm is considered a safe surgical margin (1).

In soft tissue sarcomas, reexcision is recommended in microscopic and macroscopic residual disease, and if re-excision is not possible in R2 resection, preoperative radiotherapy can also be applied to shrink the tumor. In the presence of a positive surgical margin in re-excision after preoperative RT, postoperative radiotherapy is applied to complete the total dose to 66-68 Gy. In the treatment of extremity soft tissue sarcomas, the use of arc IMRT (intensity modulated radiotherapy) or conformal RT techniques has reduced the rate of side effects secondary to radiotherapy such as edema and fibrosis.

The aim of this study is to investigate the local control results and effective predictive factors in local control of extremity soft tissue sarcomas retrospectively, that were treated with adjuvant radiotherapy.

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MATERIAL AND METHOD

The study was carried out with the permission of University of Health Science Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.06.2022, Decision No: 2022/06-124). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

Between October 2008 and January 2022, 57 patients underwent radiotherapy with the diagnosis of extremity soft tissue sarcoma in Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Radiation Oncology Clinic. 6 of the patients with metastases at the time of diagnosis and patients undergoing preoperative RT dismissed from study. All patients underwent postoperative adjuvant radiotherapy. Histopathological examination results were consistent with liposarcoma in 14 (27.5%) patients, synovial sarcoma in 9 (17.7%) patients, pleomorphic sarcoma in 7 (13.8%) patients, leiomyosarcoma in 5 (9.8%) patients, and fibrosarcoma in 4 (7.8%) patients. The histopathological subtype was not clear in 12 (23.6%) patients. In this study, the treatment outcomes of 51 patients with extremity soft tissue sarcoma who underwent postoperative adjuvant RT and the prognostic factors affecting local control and overall survival were retrospectively analyzed. The records of all patients were examined from the hospital computer system. The prognostic factors such as age, grade, tumor diameter, time between surgery and RT, surgical margin and the latest status of the patients were recorded.

Treatment Details

Wide local exicion was applied to 25 patients, marginal exicion was applied to 23 patients. Surgery type was unclear in 3 patients. Patients with tumor continuity in the surgical margin and patients with a surgical margin of less than 1 mm were considered as positive surgical margins. Patients who underwent post-operative adjuvant RT were treated with 60-68 Gy radiotherapy in 2 phases from 2 Gy /day using conformal radiotherapy technique. IMA (Ifosfamid, mesna, adriamycin) chemotherapy protocol was applied to 31.4% of the patients after radiotherapy. After the completion of the adjuvant treatments, the patients were called for control with MRI every 3 months for 2 years, every 6 months after two years, and once a year after 5 years

Statistical Analysis

SPSS version 22 was used for statistical analysis. Kaplan Meier method was used in the overall and disease-free survival analysis of the patients. Patient, tumor, and treatment-related variables were evaluated by log rank test. $P<0.05$ was considered statistically significant.

RESULTS

The follow-up period was median 46 months (range 1-135). The median age of the patients was 55 years (min: 18-max: 87). 35 (68.6%) of the patients were male and 16 (31.4%) of the patients were female. Tumor localization was in the lower extremities in 80.4%. Histopathological examination revealed grade 3 tumors for 37.3%. The tumor diameter was between 5.1-10 cm with a rate of 41.2%. The surgical margin was negative in 78.4% of cases. The median radiotherapy dose was 66 Gy (min: 50-max: 70). **Table 1** shows the general characteristics of the patients and treatment modalities.

Tablo 1. Characteristics features of the patients and treatment modalities

	n (%)
Gender	
Female	16 (31.4)
Male	35 (68.4)
Age	
18-35	5 (9.8)
36-65	35 (68.6)
>65	11 (21.6)
Pathology	
Liposarcoma	14 (27.5)
Synovial sarcoma	9 (17.7)
Pleomorphic sarcoma	7 (13.8)
Leiomyosarcoma	5 (9.8)
Fibrosarcoma	4 (7.8)
Others	12 (23.6)
Grade	
1	12 (23.6)
2	6 (11.8)
3	19 (37.3)
Unknown	14 (27.5)
Tumor Size	
≤5 cm	14 (27.5)
5.1.-10 cm	21 (41.2)
10.1-15 cm	16 (31.3)
Tumor Localization	
Upper extremity	10 (19.6)
Lower extremity	41 (80.4)
Radiotherapy Doses(Gy)	
≤60	11 (21.6)
>60	40 (78.4)
Margin Status	
Negative	40 (78.4)
Positive	11 (21.6)
Chemotherapy	
+	16 (31.4)
-	32 (62.7)
Unknown	3 (5.9)

Recurrence was detected in 5 of the patients and the mean time of recurrence was 11.6 months (min: 3-max: 27). In 10 patients developed metastasis at follow-up, the mean time until metastasis was 27 months (min: 18- max: 46). The most common organs with metastases were lung (8), bone (5), brain (1), liver (1) and adrenal (1), respectively.

The mean overall survival (OS) was 103 (min:4-max:139) months (**Figure 1**). The OS of 2, 5 and 10 years were 93%, 65% and 60%, respectively. Disease-free survival (DFS) was 97 (min:4-max:139) months (**Figure 2**). 2, 5 and 10 years of DFS were 77%, 65% and 60%, respectively.

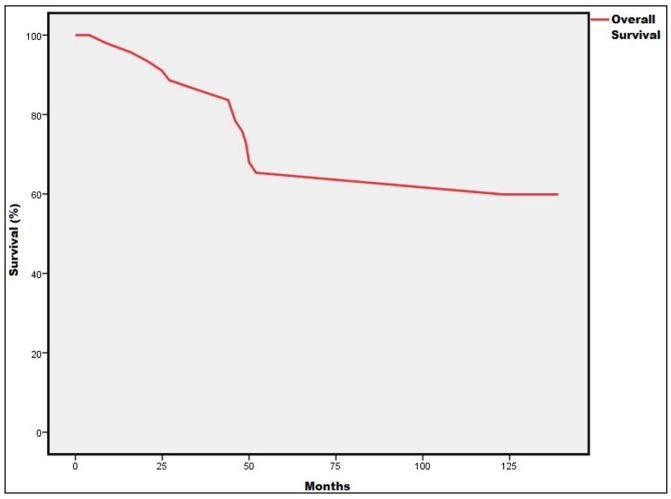

Figure 1. Overall survival

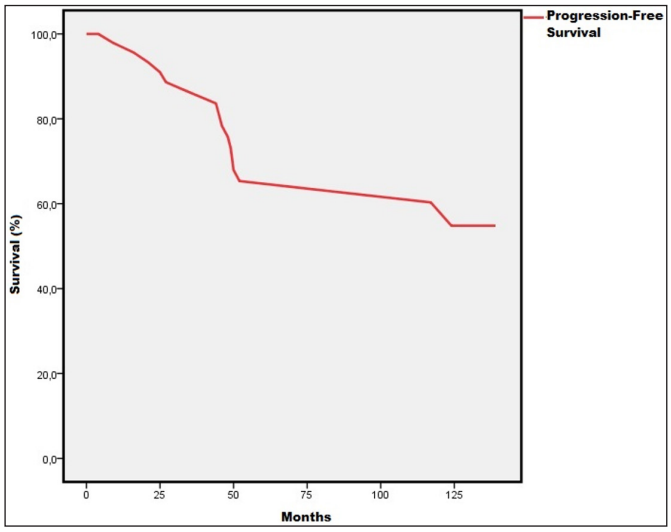

Figure 2. Event-free survival (Event: recurrence, metastasis or death)

The OS in patients ≥ 65 years old was significantly lower than in patients <65 years old (Log rank, p=0.02) (**Figure 3**). OS and DFS was significantly lower in patients undergoing chemotherapy (Log rank, p=0.037 for OS, p=0.013 for DFS). The effect of variables such as gender (p=0.77 for OS, p=0.81 for DFS), tumor T stage (AJCC version 8) (p=0.68 for OS, p=0.74 for DFS), tumor grade (p=0.40 for OS, p=0.21 for DFS), time between operation and radiotherapy (p=0.39 for OS, p=0.38 for DFS), surgical margin positivity or proximity (p=0.18 for OS, p=0.13 for DFS) on overall and disease-free survival could not be shown in our study because the limited number of patients was not sufficient to show the difference. The occurrence of recurrence, metastasis or death within 3 years after the operation is significantly higher than after 3 years (chi-square, p<0.001).

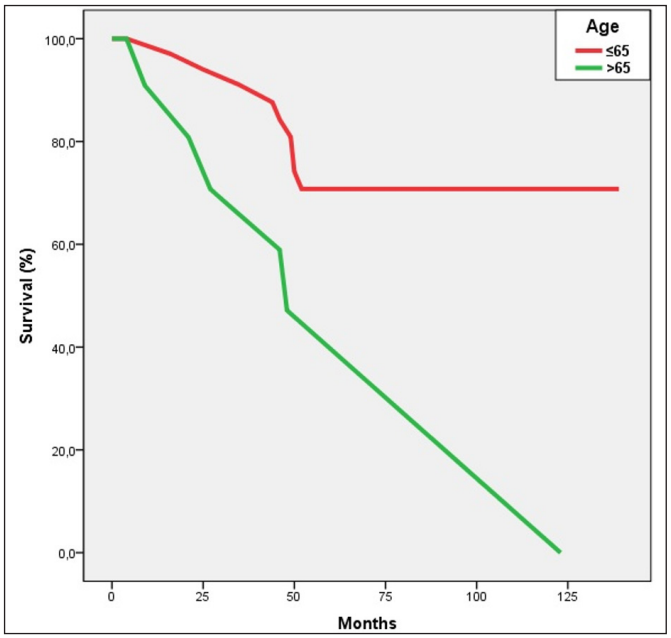

Figure 3. Overall survival by age

When the relationship between the tumor grade and recurrence was examined, the probability of recurrence of grade 3 tumors was close to significant compared to grade 1 or 2 (chi-square, p= 0.059) (**Figure 4**). All patients who recurred had grade 3 tumors and had a surgical margin ≤ 2mm. Metastasis and excitus were significantly higher in the follow-up of patients who underwent chemotherapy at one point during their treatment, while 8 of 24 patients who received chemotherapy died, 6 of 32 patients who did not receive chemotherapy died during follow-up. (chi-square, p=0.027 for metastasis, p=0.042 for excitus).

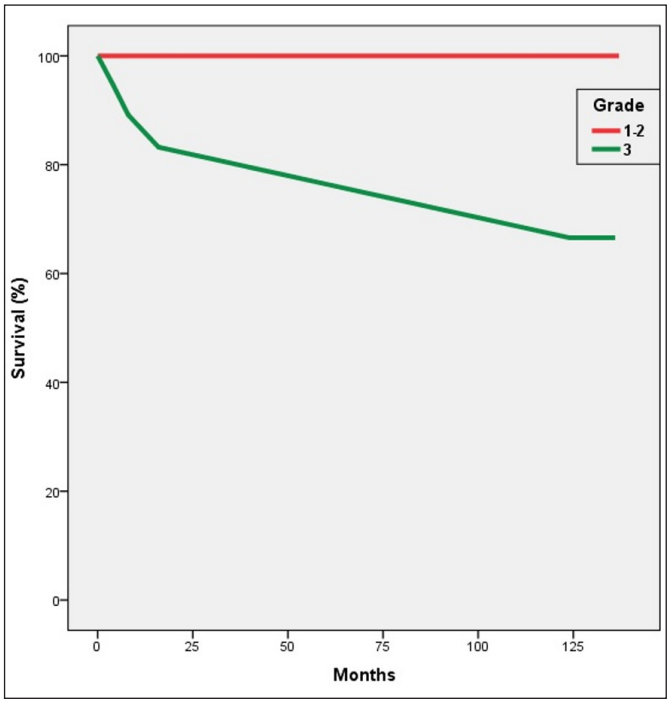

Figure 4. Recurrence-free survival by tumor grade

DISCUSSION

Undifferentiated pleomorphic sarcoma, liposarcoma and leiomyosarcoma are the most common cases in adult soft tissue sarcomas (7). In our study, liposarcoma (27.5%) was the most common histopathological subtype followed by synovial sarcoma (17.7%) and pleomorphic sarcoma (13.8%).

Surgical resection is the primary treatment in soft tissue sarcomas and radiotherapy is applied in the preoperative or postoperative period. The standard surgical treatment is wide excision with a negative surgical margin (R0). However, marginal excision can also be performed in tumors close to neurovascular structures because there is difficulty to provide a negative surgical margin. Sometimes, preoperative radiotherapy is applied to the patients to shrink the tumor before surgery. In our study, all patients underwent postoperative adjuvant-conformal radiotherapy after limb-sparing surgery.

Local control rates have been improved with limb-sparing surgery and adjuvant RT in soft tissue sarcomas in some studies (1,7-11). In two randomized studies, the contribution of adjuvant RT to local control in patients with soft tissue sarcoma who underwent limb-sparing surgery was mentioned (2,12). In a prospective-randomized study by Yang et al. (2), it was mentioned that adjuvant RT was effective in reducing local relapses without affecting overall survival rates. In the study of Gronchi et al. (13) it was stated that local control directly affects survival. In our study, high local control rates were obtained with adjuvant RT. The number of patients with local recurrence was 5 (9.9%) and the mean time of recurrence development was 11.6 months (min 3-max.27 months). We think that the use of conformal radiotherapy technique and high radiotherapy doses (66-68 Gy) were effective in our low local recurrence rate.

In our study, the mean overall survival was 103 (min:4-max:139) months and the overall survival of 2, 5 and 10 years were 93%, 65% and 60%, respectively. Disease-free survival was 97 (min:4-max:139) months. Disease-free survival of 2, 5 and 10 years were 77%, 65%, and 60%, respectively. Our results is consistent with the literature.

Tumor grade is very important in patients with soft tissue sarcoma in terms of both local recurrence and distant metastasis (3,6). In our study, grade 3 tumors were the majority (37.3%) of the patients. Local failure was significantly higher in grade 3 tumors (p=0.05). All the patients with local recurrence (5 patients) had grade 3 tumors.

Since the tumor diameter is large in soft tissue sarcomas and the risk of recurrence and distant metastasis is high in high-grade tumors, these tumors may benefit from chemotherapy (14). In addition, in some studies, the role of chemotherapy in the treatment of soft tissue sarcomas is still controversial. A meta-analysis by Pervaiz et al. (15) showed only a marginal efficacy with respect to local recurrence, distant recurrence and overall survival. In the study of Woll et al. (16) there was no difference in overall survival and recurrence-free survival with adjuvant external RT and doxorubucin-ifosfamide chemotherapy. In the randomized phase-2 study of Stone et al. (17) the efficacy of neoadjuvant chemotherapy in adult soft tissue sarcomas was investigated and no significant survival advantage was seen.

In our study, adjuvant chemotherapy was applied to 16 (31.4%) patients. In univariate analysis, overall (p=0.037) and disease-free survival (p=0.013) were statistically lower in patients undergoing adjuvant chemotherapy. This can be due to the fact that metastasis and mortality rates are higher in these patient group since chemotherapy was generally applied in higher risk patients.

In our study, the rate of patients ≥65 years old was 21.6% and overall survival in these patients was significantly lower compared to patients <65 years old in univariate analysis (p=0.02). This may be due to the high incidence of comorbid diseases in elderly patients, higher rate of non-cancer deaths and difficulties in treatment applications to older patients.

In soft tissue sarcomas, surgical margin is the most important risk factor for local recurrence (3-6). According to the NCCN guidelines, 10 mm surgical margin is considered safe (1). In our study, due to the low number of patients, the effects of surgical margin on disease-free and overall survival could not be statistically evaluated but all patients who recurred had surgical margin ≤ 2mm. Surgical margin is adjacent in 2 patients and <1mm in 1 patient .

In the study of Falk et al. (18,19) ablation therapies such as surgery, radiofrequency and radiotherapy had a significant survival advantage in metastatic sarcomas compared to patients who did not receive these treatments (p=0.0001). In the study of Lindsay et al. (20), it was shown that stereotactic body RT provided a survival advantage in lung metastases.

In our study, the rate of patients with metastases was 19.6% (10 patients) and lung metastasis was the most common. While metastasectomy was performed in 4 out of 8 patients who devoleped lung metastases, whole brain radiotherapy (30 gy) was applied to 1 patient with brain metastasis. Additionally recurrence, metastasis or death in the first 3 years after operation was significantly higher than after 3 years (p<0.001). These findings support the need for close follow-up of the patients, especially in the first 3 years.

CONCLUSION

While favorable local control results are obtained with adjuvant high dose-conformal radiotherapy in extremity sarcomas, close follow up is important for distant metastasis and local recurrence, especially in the first 3 years.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Science Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Researchs Ethics Committee (Date: 23.06.2022, Decision No: 2022/06-124).

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. NCCN (National Comprehensive Cancer Network) Guidelines Version 2.2022 Soft Tissue Sarcoma. Available Online: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
2. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998; 16: 197-203.
3. Biau DJ, Ferguson PC, Chung P, et al. Local recurrence of localized soft tissue sarcoma: a new look at old predictors. Cancer 2012; 118: 5867-77.
4. Sampo M, Tarkkanen M, Huuhtanen R, Tukiainen E, Bohling T, Blomqvist C. Impact of the smallest surgical margin on local control in soft tissue sarcoma. Br J Surg 2008; 95: 237-43.
5. Potter BK, Hwang PF, Forsberg JA, et al. Impact of margin status and local recurrence on soft-tissue sarcoma outcomes. J Bone Joint Surg Am 2013; 95: e151.
6. Sugiura H, Nishida Y, Nakashima H, Yamada Y, Tsukushi S, Yamada K. Surgical procedures and prognostic factors for local recurrence of soft tissue sarcomas. J Orthop Sci 2014; 19: 141-9.
7. Casali PG, Abecassis N, Aro HT, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29: 51-67.
8. Beane JD, Yang JC, White D, Steinberg SM, Rosenberg SA, Rudloff U. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Ann Surg Oncol 2014; 21: 2484-9.
9. DeLaney TF, Trofimov AV, Engelsman M, Suit HD. Advanced-technology radiation therapy in the management of bone and soft tissue sarcomas. Cancer Control 2005; 12: 27–35.
10. Alektiar KM, Brennan MF, Healey JH, Singer S. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. J Clin Oncol 2008; 26: 3440-4.
11. Hoefkens F, Dehandschutter C, Gestel DV, et al. Soft tissue sarcoma of the extremities; pending questions on surgery and radiotherapy. Radiat Oncol 2016; 11: 136.
12. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996; 14: 859-68.
13. Gronchi A, Lo Vullo S, Colombo C, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. Ann Surg 2010; 251: 506-11.
14. Look Hong NJ, Hornicek FJ, Harmon DC, et al. Neoadjuvant chemoradiotherapy for patients with high-risk extremity and truncal sarcomas: a 10-year single institutionretrospective study. Eur J Cancer 2013; 49: 875-83.
15. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008; 113: 573-81.
16. Woll PJ, Reichardt P, Le Cesne A, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. Lancet Oncol 2012; 13: 1045-54.
17. Stone P, Rees E, Hardy JR. A randomised phase II study on neo-adjuvant chemotherapy for "high-risk" adult soft-tissue sarcoma. Eur J Cancer 2001; 37: 1096-103.
18. Falk AT, Moureau-Zabotto L, Ouali M, et al. Effect on survival of local ablative treatment of metastases from sarcomas: a study of the french sarcoma group. Clin Oncol 2015; 27: 48-55.
19. Cammelli S, Cotesi A, Buwenge M, et al. The role of Radiotherapy in adult soft tissues sarcoma of the extremities. Eur J Orthop Surg Traumatol 2021; 31: 1583-96.
20. Lindsay AD, Haupt EE, Chan CM, et al. Treatment of sarcoma lung metastases with stereotactic body radiotherapy. Sarcoma 2018; 2018: 9132359.

Original Article

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An automated diabetic retinopathy disorders detection model based on pretrained MobileNetv2 and nested patch division using fundus images

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ABSTRACT

Aim: Fundus images are very important to diagnose some ophthalmologic disorders. Hence, fundus images have become a very important data source for machine-learning society. Our primary goal is to propose a new automated disorder classification model for diabetic retinopathy (DR) using the strength of deep learning. In this model, our proposed model suggests a treatment technique using fundus images.

Material and Method: In this research, a new dataset was acquired and this dataset contains 1365 Fundus Fluorescein Angiography images with five classes. To detect these disorders automatically, we proposed a transfer learning-based feature engineering model. This feature engineering model uses pretrained MobileNetv2 and nested patch division to extract deep and exemplar features. The neighborhood component analysis (NCA) feature selection function has been applied to choose the top features. k nearest neighbors (kNN) classification function has been used to get results and we used 10-fold cross-validation (CV) to validate the results.

Results: The proposed MobileNetv2 and nested patch-based image classification model attained 87.40% classification accuracy on the collected dataset.

Conclusions: The calculated 87.40% classification accuracy for five classes has been demonstrated high classification accuracy of the proposed deep feature engineering model.

Keywords: Diabetic retinopathy, fundus image processing, biomedical image classification, artificial intelligence

INTRODUCTION

Diabetic Retinopathy (DR) is specific angiopathy involving retinal capillaries, arterioles, and venules, which occurs as a result of hyperglycemia, insulin deficiency, or insulin resistance (1, 2). The term diabetic retinopathy is used to describe microvascular abnormalities (microaneurysms, hemorrhage, exudates, neovascularization (NVE, NVD, preretinal/vitreous hemorrhage) found in clinical examination or fundus images, and according to the presence of these findings in the fundus, Nonproliferative Diabetic retinopathy (NPDR) and Proliferative diabetic retinopathy (PDR). It is divided into two main groups diabetic retinopathy (PDR). Macular edema is also one of the important causes of low vision in diabetic patients and can be found together with NPDR or PDR (3-5). Diabetic retinopathy (DR) is a common and serious complication of diabetes that can result in blindness. It is known to affect approximately 100 million people worldwide, and it will affect an estimated 600 million people in 2040. Studies have shown that with early intervention of DR, good results can be achieved in preventing the development of the disease and the rate of blindness can decrease significantly (6-8). Early scanning is very important for diagnosis and timely intervention. Clinical DR screening and diagnosis are typically based on Color Fundus Photograph (CFP) or Fundus Fluorescein Angiography (FFA) images (9). CFP is a rapid, non-invasive, and widely used method for DR screening (10). However, FFA can detect typical pathological changes such as

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microaneurysms, non-perfusion sites, and vascular leakage, and provide dynamic information about the retinal vascular structure that CFP cannot identify. FFA is a more powerful tool than CFP in fully assessing the severity of DR, which directly guides individual treatment plans and plays an important role in the diagnosis of DR (11). Many studies have confirmed the efficacy of lowering HbA1c level with the stability of tight glycemic index, control of blood pressure, and lipid profile in stopping DR progression (12-14). However, in cases where progression cannot be prevented, various treatments are applied to prevent vision loss. Laser photocoagulation, one of these treatment methods, is used to treat two main complications in diabetes: 1) neovascularization of the retina and 2) severe or clinically significant macular edema (15). Panretinal laser photocoagulation (LPC) is an effective method for regressing neovascularization performed in sessions (5). Apart from this, intravitreal injections and various lasers such as focal, grid, and subluminal lasers are applied in the treatment of macular edema. In resistant cases that do not respond to all these treatments, pars plana vitrectomy is applied (16).

Artificial intelligence (AI) is a branch of computer science in which machines mimic the cognitive function of the human mind. Artificial intelligence has widespread use in health and medical sciences. AI has been used in medicine since the early 1950s when doctors sought to improve the accuracy of their diagnoses using computer-assisted algorithms (17). AI has been applied in image-based medical fields such as Radiology and Ophthalmology, as it is suitable for processing complex images (18, 19). Various studies have been conducted in the field of ophthalmology to assist in the diagnosis of diseases such as DR, glaucoma, age-related macular degeneration, and retinopathy of prematurity (20). AI is planned to be used as a potential alternative to DR screening to help reduce the burden on ophthalmologists and overcome barriers with telemedicine. AI helps the right patients be seen at the right time and managed in the right place. However, there are shortcomings in using artificial intelligence to optimize DR management. In this research, we collected a new FFA dataset and we proposed a machine learning model to propose treatment techniques for helping medical professionals.

Motivation and Our Model

In the last decade, an important image classification methodology has been presented and this methodology is named deep learning. By proposing deep learning, great advances have been made in the field of computer vision. Also, computer vision models have been applied to biomedical images to generate/develop intelligence assistants. In this research, we proposed a pretrained deep learning – we used a pretrained MobileNetv2 (21) – based image classification model to contribute to DR disorders classification. Fundus images have circular structures. Therefore, we used four nested patches to extract features. Moreover, the last pooling layer of the pretrained MobileNetV2 has been used to extract deep features. The used layer (global average pooling layer of the MobileNetV2) has been applied to each patch and the features have been generated. In the feature selection layer, we used NCA (22) selector and the top 512 features have been selected. These 512 features have been used as input for the kNN classifier. The rough block diagram of our proposal is demonstrated in **Figure 1**.

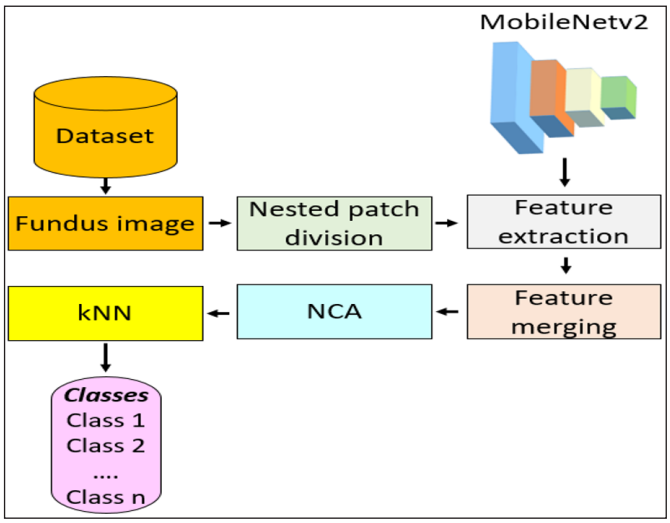

Figure 1. Block diagram of the proposed MobileNetv2 and NCA-based fundus image classification based model

Contributions

In this research, we collected a new Fundus Fluorescein Angiography images dataset to classify groups of the DR and we presented a deep feature-based model. The contributions of this research are given below.

Contributions:

- DR is one of the most commonly seen ophthalmologic disorders and groups of this disorder are very important to the selection cure method. In the literature, there are many PDR, NPDR, and healthy fundus classification models but there is no PDR/NPDR categorization/cure proposal model (machine learning based) in the literature as our knowledge.
- Deep networks are the flagships of computer vision models. Thus, the usage area of the deep networks is wide. Moreover, by using transfer learning, users/developers/scientists have used advantages of the deep networks with low time complexity. In this research, we proposed a new patch-based deep feature engineering image classification model. In the literature, fixed-size patches generate exemplar features. However, fundus images have a circular structure. Thus, we used nested patch division to detect local abnormalities.

Further, we used a lightweight CNN – MobileNetv2 – to generate features. Our proposal attained 87.40% accuracy on the used dataset.

MATERIAL AND METHOD

The study was carried out with the permission of Fırat University, Non-Interventional Research Ethics Board (Date: 13.03.2022 Decision No: 2022/04-10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. We collected a new FFA image dataset from Fırat University Hospital. This dataset contains 1365 FFA images with five categories and these categories are (i) NPDR+macular edema and intravitreal injection/ macular laser treatment are recommended, (ii) PDR without macular edema and retinal laser recommended, (iii) PDR+macular edema and intravitreal injection/ macular laser+retinal laser recommended, (iv) Metabolic regulation without ocular treatment –NPDR patient without macular edema requiring follow-up, early stage and (v) healthy. The format of these FFA images is dicom and we converted them to jpg images. These FFA images have variable sizes. In our proposal, we resized these images to 224 × 224 sized images. The sample images are given in **Figure 2**.

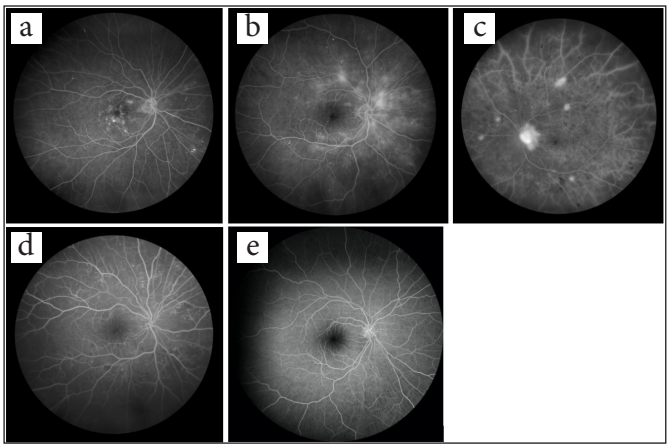

Figure 2. Sample FFA images from each category. **(a)** Intravitreal injection/macular laser **(b)** Retinal laser **(c)** Intravitreal injection/ macular laser+ Retinal laser **(d)** Metabolic regulation without ocular treatment **(e)** Healthy

Distributions of the FFA images are also given in **Table 1**.

Table 1. Properties of the collected FFA dataset

Number	Class	Number of images
1	Intravitreal injection/macular laser (II/ML)	126
2	Retinal laser (RL)	339
3	Intravitreal injection/macular laser+ Retinal laser (II/ML+RL)	372
4	Metabolic regulation without ocular treatment (MR-OT)	179
5	Healthy	349
Total		1365

The Proposed Model

We proposed a new generation model of deep transfer learning-based fundus image classification model. This model is directly about feature engineering since it has feature extraction, feature selection, and classification layers. Nested patch division and pretrained MobileNetv2 have been used in the feature extraction layer. The used MobileNetv2 was trained on the ImageNet1K (23) (this dataset contains approximately 1.3 million images with 1000 object categories) and the last global average pooling layer has been utilized as a feature extractor. We generated four nested patches in this section since the sizes of our patches are 56 × 56, 112 × 112, 168 × 168, and 224 × 224. These patches have been generated from a fundus image with a size of 224 × 224. The top 512 features of the generated features have been chosen by deploying the NCA feature selection function. The chosen 512 features have been utilized as input of the kNN (24) classifier. The schematic expression of the proposed nested MobileNetV2-based model has been demonstrated in **Figure 3**.

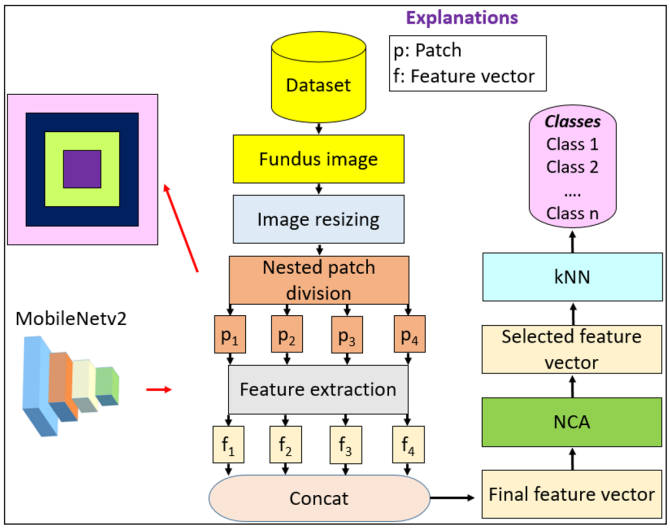

Figure 3. Graphical explanation of the proposed MobileNetv2-based fundus image classification model

In order to better express the proposed model, the steps of this model are given below.

Step 1: Read/load each image from the collected fundus angiography dataset.

Step 2: Resize each image to 224 × 224.

Step 3: Create nested patches from the resized image. This process is given below.

$$p_k = Img(c - s_k + 1 : c + s_k, c - s_k + 1 : c + s_k, l), l \in \{1,2,3\}$$
$$k \in \{1,2,3,4\}, s \in \{28,56,84,112\}, c = 112 \quad (1)$$

where Img defines the used fundus image, p_k represents kth patch and s is an increasing array to generate nested patches.

Step 4: Extract deep features from the generated patches in Step 3.

$$f_k = Mv2(p_k, GAP) \quad (2)$$

Herein, f_k defines kth feature vector with a length of 1280, $Mv2(.)$ pretrained MobileNetv2, and GAP represents the global average pooling layer and we used this layer to extract features.

Step 5: Merge/concatenate the generated feature vectors to obtain the final feature vector.

$$F(j + 1280 \times (k-1)) = f_k(j), j \in \{1,2,\ldots,1280\} \quad (3)$$

Here, F defines a merged feature vector with a length of 5120 (=1280×4).

Step 6: Apply NCA to these generated 5120 features and select the top 512 out of 5120 features.

Step 7: Classify the selected 512 features using the kNN classifier with 10-fold cross-validation. The attributes of the kNN classifier are given as follows. k is 1, distance metric: L1-norm, and voting is no-voting.

RESULT

We proposed a new MobileNetv2-based model and this model applied to the collected fundus angiography images. In the classification, the kNN classifier was used to get classification results. We used 10-fold cross-validation for validation. Furthermore, we used a simple configure computer (this computer has a 3.6 GHz processor, 16 GB memory, and Windows 10.1 operating system) and our used programming environment is MATLAB 2021a. Firstly, the pretrained MobileNetv2 was installed in MATLAB 2021a. A deep feature generation function was created using this library. Moreover, we created the main function to implement our proposed model.

In order to evaluate the classification ability of our proposal, we used unweighted average recall (UAR), unweighted average precision (UAP), and overall F1 score (25, 26). Further, we gave class-wise recall, precision, and F1 scores. The calculated confusion matrix of this model is also given in **Figure 4**.

According to this confusion matrix (see **Figure 4**), our model was tested on a fundus angiography dataset with five classes. These classes are enumerated from 1 to 5. These classes are 1: Intravitreal injection/macular laser, 2: Retinal laser, 3: Intravitreal injection/macular laser+ Retinal laser, 4: Metabolic regulation without ocular treatment, and 5: healthy. The overall results using this confusion matrix are listed in **Table 2**.

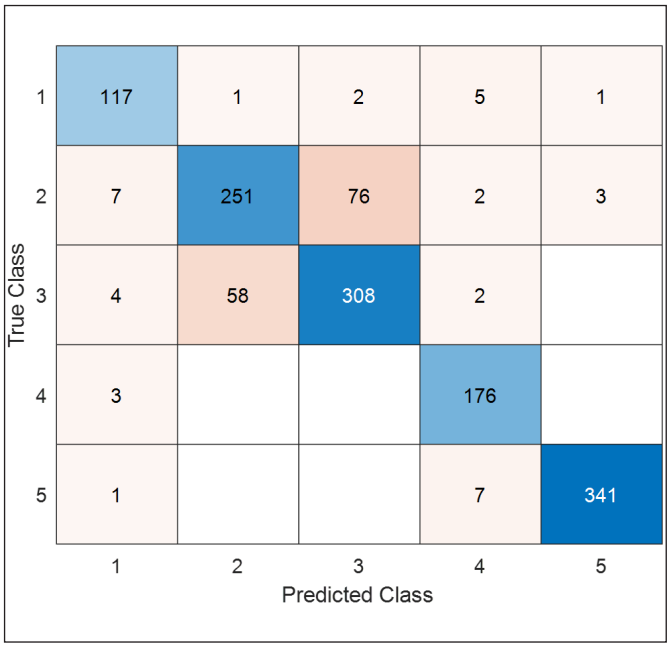

Figure 4. The calculated confusion matrix

Table 2. Overall results (%) of the proposed MobileNetv2-based model

Performance metric	Result (%)
Accuracy	87.40
Unweighted average recall	89.15
Unweighted average precision	87.98
F1-score	88.49

Class-wise performances of the proposed model are demonstrated in **Figure 5**.

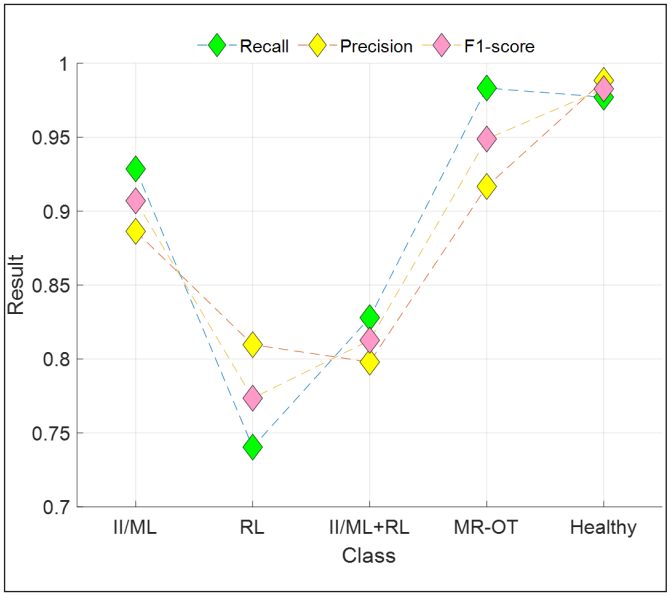

Figure 5. Class-wise results

Figure 5 demonstrated that the best accurate class is a healthy class. The worst two classes are Retinal laser and Intravitreal injection/macular laser+ Retinal laser since these types of disorders are very close to each other.

DISCUSSION

In this work, we have proposed a cure proposal mechanism using fundus angiography images. We used a deep transfer learning model and this model uses MobileNetV2 and nested patch division. In the feature extraction phase, 5120 features have been extracted from each fundus angiography image. By deploying NCA, 512 out of 5120 features have been selected. These features have been classified using a kNN classifier with a 10-fold CV. Our model attained 87.40% classification accuracy on the collected dataset. Moreover, class-wise results were calculated. According to this calculation (class-wise result calculation), results of the Retinal laser and Intravitreal injection/macular laser+ Retinal laser are lower than 85%. Results of other classes were over 85% (see **Figure 5**).

- As our knowledge, we are the first team to propose an automated classification model to propose treatment techniques using fundus angiography images. The important points of this research are listed below.
- Transfer learning was used for feature extraction. Thus, the time complexity of this model is low.
- Our proposed model attained 87.40% classification accuracy. Moreover, a 10-fold CV supports robust results calculation.
- This model is a simple and effective model.
- We used methods with default settings. There is no fine-tuning operation. Thus, this model is a cognitive model.
- The application of this model is very easy. Other image classification problems can be solved through this model.
- An intelligent cure proposal assistant can be used using our model in the near future.
- We collected this dataset from a single medical center. By collaborating with more medical centers, larger datasets can be collected.

Our study has some limitations. First, multimodal imaging modalities such as optical coherence tomography (OCT) and OCT-Angiography were not used. Second, the study was conducted in a single center. Finally, the number of samples was small.

CONCLUSION

In this research we proposed a new automated disorder detection model using computer vision model. We collected a FFA dataset and this dataset contains five classes. The collected FFA images were utilized as input of the proposed nested-patch based model. The nested patches have been used to generate features from local areas. These generated all feature vectors were concatenated to obtain final feature vector. The top features were selected by deploying NCA. The selected feature vector was utilized as input of the kNN classifier. Our proposed model attained 87.40% classification accuracy for the collected FFA dataset. This result obviously depicted that the presented nested patch-based deep feature engineering model is a good model for FFA classification.

Soon, we are planning to develop an automated disorder detection application using FFA images. Therefore, we will use attention-based models in the near future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Fırat University, Non-Interventional Research Ethics Board Decisions (Date: 13.03.2022 Decision No: 2022/04-10).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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. Shome SK, Vadali SRK. Enhancement of diabetic retinopathy imagery using contrast limited adaptive histogram equalization, Int J Computer Sci Inform Technol 2011; 2: 2694-9.
2. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review, Jama, 2007; 298: 902-16.
3. Solomon SD, Goldberg MF. ETDRS grading of diabetic retinopathy: still the gold standard? Ophthalmic Research 2019; 62: 190-5.
4. Wu L, Fernandez-Loaiza P, Sauma J, Hernandez-Bogantes E, Masis M. Classification of diabetic retinopathy and diabetic macular edema, World J Diabetes 2013; 4: 290-4.
5. Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic retinopathy preferred practice pattern®, Ophthalmology 2020; 127: 66-145.
6. Ogurtsova K, Fernandes JdaR, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040, Diabetes Research Clin Practice 2017; 128: 40-50.
7. Lian F, Wu L, Tian J, et al. The effectiveness and safety of a danshen-containing Chinese herbal medicine for diabetic retinopathy: a randomized, double-blind, placebo-controlled multicenter clinical trial. J Ethnopharmacol 2015; 164 : 71-7.
8. Tan F, Chen Q, Zhuang X, et al. Associated risk factors in the early stage of diabetic retinopathy, Eye and Vision 2019; 6: 1-10.
9. Cole ED, Novais EA, Louzada RN, Waheed NK. Contemporary retinal imaging techniques in diabetic retinopathy: a review, Clin Experime Ophthalmol 2016; 44: 289-99.
10. Kwan CC, Fawzi AA. Imaging and biomarkers in diabetic macular

edema and diabetic retinopathy, Current Diabetes Reports 2019; 19: 1-10.

11. Gao Z, Jin K, Yan Y, et al. End-to-end diabetic retinopathy grading based on fundus fluorescein angiography images using deep learning, Graefe's Archive Clin Experime Ophthalmol 2022; 260: 1663-73.
12. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-12.
13. Sacks FM, Hermans MP, Fioretto P, et al. Association between plasma triglycerides and high-density lipoprotein cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes mellitus: a global case–control study in 13 countries. Circulation 2014; 129: 999-1008.
14. Morton J, Zoungas S, Li Q, et al. Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: results of the ADVANCE study, Diabetes Care 2012; 35: 2201-6.
15. El Rami H, Barham R, Sun JK, Silva PS. Evidence-based treatment of diabetic retinopathy, in: Seminars in Ophthalmology, Taylor & Francis, 2017, pp. 67-74.
16. Akkaya S, Acikalin B, Asilyazici E, Yilmaz A, Yamic M, Kocapinar Y. Diagnosis and treatment of diabetic retinopathy. Retina-Vitreus/Journal of Retina-Vitreous 2018; 27: 390-401
17. Secinaro S, Calandra D, Secinaro A, Muthurangu V, Biancone P. The role of artificial intelligence in healthcare: a structured literature review, BMC Medical Informatics and Decision Making, 2021; 21: 1-23.
18. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJ. Artificial intelligence in radiology. Nature Reviews Cancer 2018; 18: 500-10.
19. Hipwell J, Strachan F, Olson J, McHardy K, Sharp P, Forrester J. Automated detection of microaneurysms in digital red-free photographs: a diabetic retinopathy screening tool, Diabetic Medicine 2000; 17: 588-94.
20. Padhy SK, Takkar B, Chawla R, Kumar A. Artificial intelligence in diabetic retinopathy: a natural step to the future, Indian J Ophthalmol 2019; 67: 1004-9.
21. Sandler M, Howard A, Zhu M, Zhmoginov A, Chen L.-C. Mobilenetv2: inverted residuals and linear bottlenecks, in: Proceedings of the IEEE conference on computer vision and pattern recognition. CVPR 2018; 4510-20.
22. Goldberger J, Hinton GE, Roweis S, Salakhutdinov RR. Neighbourhood components analysis. Advances in Neural Information Processing Systems 2004; 17: 513-20.
23. Krizhevsky A, Sutskever I, Hinton GE. Imagenet classification with deep convolutional neural networks. Communications of the ACM 2017; 60: 84-90.
24. Peterson LE. K-nearest neighbor. Scholarpedia 2009; 4: 1883.
25. Warrens MJ. On the equivalence of Cohen's kappa and the Hubert-Arabie adjusted Rand index. J Classification 2008; 25: 177-83.
26. Powers DM. Evaluation: from precision, recall and F-measure to ROC, informedness, markedness and correlation. arXiv preprint arXiv 2020: 2010.16061.

Original Article

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Plate osteosynthesis for proximal humerus fractures through a deltoid-split approach under traction in lateral decubitus position: preliminary results

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ABSTRACT

Aim: We aimed to present deltoid split approach under traction in lateral decubitus position that we perform for the treatment of proximal humerus fractures (PHFs) and to present the preliminary surgical and clinical outcomes of our patients.

Material and Method: Twelve patients who underwent plate osteosynthesis through a deltoid split approach under traction in lateral decubitus position between May 2019 and January 2021 were evaluated. Patient demographics, Neer classification, and time from injury to surgery were collected in all patients preoperatively. Radiation exposure time and operating time was recorded intraoperatively. Radiological outcomes were assessed, including time to union, and neck-shaft angle. Functional outcomes were evaluated using the Constant score at the minimum 12-month follow-up.

Results: Twelve patients (5 male, 7 female) were evaluated with a mean age 58.6±10.7 years (range, 32 to 72 years) at the time of surgery. The mean follow-up period was 117.4±3.8 months). The mean operation time was 60.7±15.2 min (range, 44 to 92 min). The mean radiation exposure time was 6.1±3.0 s (range, 3.3 to 14.2 s). Fracture union was observed in all patients at mean 14.6±2.5 weeks (range, 8 to 20 weeks). The mean neck-shaft angle after the union was 134.5±3.4 degrees (range, 124 to 143 degrees). The mean Constant score was at the final follow-up was 76.4±8.7 (range, 63 to 90).

Conclusion: Patient positioning in the lateral decubitus position under traction can be considered as a safe, reliable, and reproducible method in selected patients with PHFs.

Keywords: Proximal humerus fracture, fixation, traction, lateral decubitus

INTRODUCTION

The management of the proximal humeral fractures (PHFs) remains a technical challenge to internal fixation, based on complex fracture configuration, appropriate approach selection, and anatomical reduction (1-3). However, the potential effect of patient positioning on surgical outcomes has not been evaluated. The effect of a traction table that can provide or improve reduction is indisputable for the proximal femur fractures (4). Why should not this also be considered for the PHFs?

Although there continues to be controversy regarding the optimal treatment of PHFs, anatomical reduction is an essential for the fixation of the PHFs (5,6). The purpose of this study was to describe a lateral decubitus position under traction that led to facilitate anatomical reduction in the treatment of the PHFs and to present the preliminary surgical and clinical outcomes. We hypothesize that this position will provide better anatomical reduction and would shorten the operating time compared with previously reported literature.

MATERIAL AND METHOD

This retrospective study was carried out with the permission of the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 18.05.2022, Decision No: 2022/240). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who underwent internal fixation of a proximal humerus fracture between 2019 and 2021 were identified.. A total of 12 patients who underwent plate osteosynthesis through a deltoid split approach under traction in lateral decubitus position were included in this study. All patients had Neer type two-, three- or four-part PHFs (7). Time from injury to surgery, radiation exposure time, operation time, union rate, time to union, neck-shaft angle and Constant score were extracted in all patients retrospectively and the data set was created.

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Surgical Technique

All patients were placed in a lateral decubitus position under general anesthesia. To keep the patient in a stable position, ventral and dorsal supports were used. To avoid pressure injuries, all bony points were padded. The operative extremity is wrapped in an elastic bandage with care being taken not to compress the hand to avoid any neurovascular complications. Then, the involved upper extremity was secured at 30 degrees of abduction and axial traction was performed with 3 kg hanging from the forearm to saline stand via a pulley. The C-arm was positioned medially and laterally to achieve the projection of the involved shoulder (**Figure 1**). The shoulder was draped in a sterile manner.

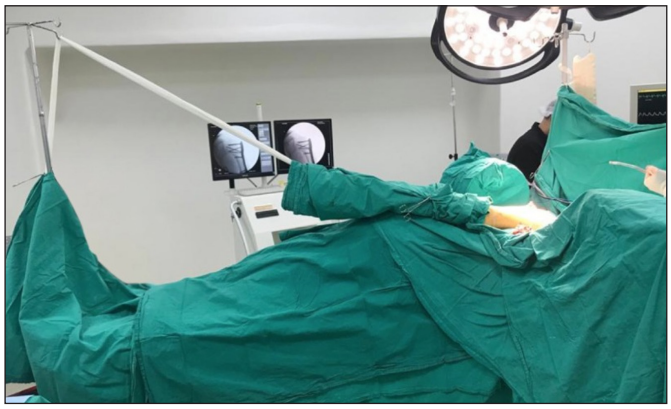

Figure 1. The operative arm is placed into the traction device and traction is applied with a 3 kg. Intraoperative view of patient positioning.

A fluoroscopy control was performed before the incision and an acceptable reduction due to traction was observed in most cases. Then, bony landmarks and the location of axillary nerve were marked with a surgical pen. A skin incision of 6-8 cm was made on the anterolateral aspect of the shoulder. The deltoid muscle was split, and the neurovascular bundle was identified by digital palpation. The distance from the axillary nerve to the tip of the acromion varies from 5 to 7 cm. Two windows were created proximal and distal to the axillary nerve. The proximal window was used for reduction. Traction sutures were placed in tuberosity fragments. Humeral head was reduced with use of a blunt dissector and calcar continuity was ensured under fluoroscopy control (**Figure 2**). The sagittal alignment was also directly provided by the traction effect. A proximal humerus internal locking plate was meticulously placed under neurovascular bundle after provisional reduction of the fracture. The plate position was confirmed, and a cortical screw was inserted into the shaft through the oval hole. Then, the locking screws were placed into the superior holes and the distal shaft holes of plate, respectively. Finally, the calcar screws were inserted via proximal and distal mobilization of the axillary nerve and fluoroscopy control was performed (**Figure 3**). Then, the traction sutures were passed and knotted through the side holes of the plate. The deltoid muscle fibers were approximated, and the wound was closed.

Postoperative Follow-up

All patients wore a shoulder sling in 30 degree of abduction for six weeks. Active elbow and wrist motion were encouraged immediately after surgery. Active-assisted shoulder range of motion (ROM) exercises were started at four weeks. Active ROM, strengthening and weight bearing were permitted gradually at six to eight weeks postoperatively when bone healing was seen.

RESULTS

Twelve patients (5 male, 7 female) were evaluated with a mean age 58.6±10.7 years (range, 32 to 72 years) at the time of surgery. The mean follow-up period was 17.4±3.8 months (range 12 to 24 months). Detailed patient demographics are shown in **Table 1**.

Table 1. Patient demographics

Characteristic	Data
Number of Patients	12
Age, yr, mean±SD (Range)	55.4±10.4 (32-69)
Sex, M/F, n	5/7
Side, R/L, n	6/6
BMI, kg/m2, mean±SD (Range)	29.1±3.4 (22.5-37.3)
Time from injury to surgery, d, mean±SD (Range)	1.2±0.4 (0-2)
Follow-up time, mo, mean±SD (Range)	19.2±5.2 (12-28)

BMI: body mass index; F: female; M: male; L: left; R: right; SD: standard deviation

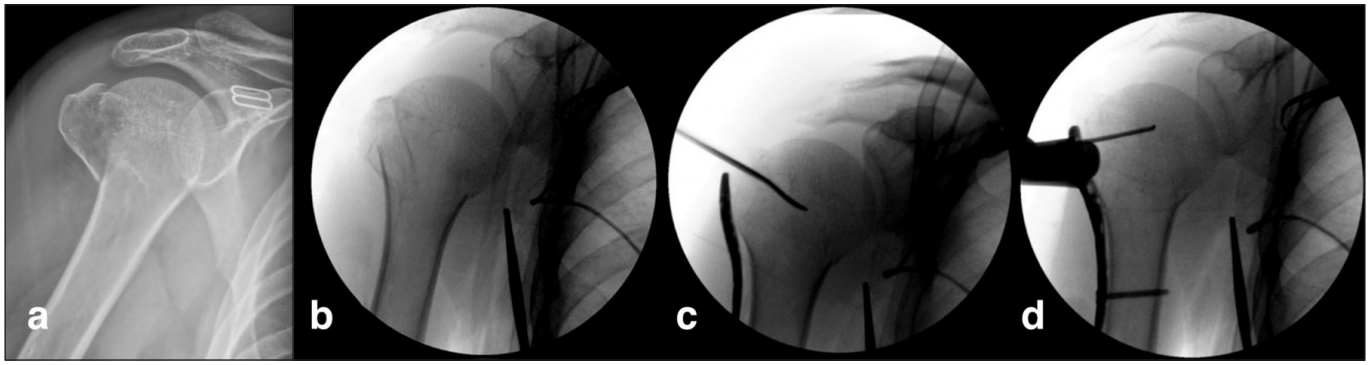

Figure 2. Patient with Neer type III proximal humerus fracture a pre-operative X-ray (a), intra-operative fluoroscopy views, preliminary reduction under traction (b), a proximal humerus plate is inserted, then calcar continuity provided by elevator (c), one cortical screw is placed distally and locking screws are placed into head (d).

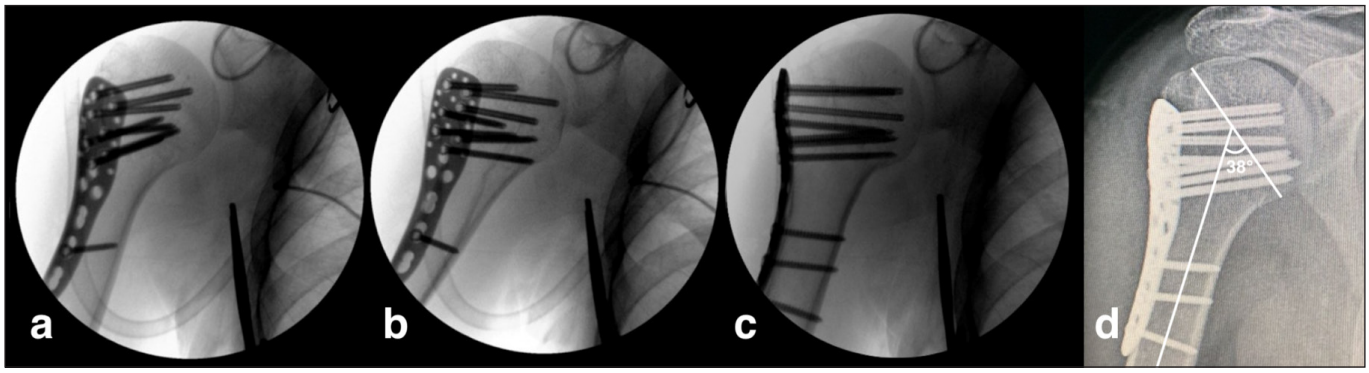

Figure 3. Internally (a), externally (b) and neutral (c) rotation fluoroscopy views of proximal humerus end of the operation. 1- year postoperatively radiograph is shown with 142 degrees of neck-shaft angle (d).

The mean operation time was 60.7±15.2 min (range, 44 to 92 min). Patient positioning and setting up for fluoroscopy were not recorded in the operation time. The mean radiation exposure time was 6.1±3.0 s (range, 3.3 to 14.2 s). Fracture union was observed in all patients at mean 14.6±2.5 weeks (range, 8 to 20 weeks). The mean neck-shaft angle after the union was 134.5°±3.4 (range, 124° to 143°). All patients were showed good to excellent clinical outcomes. Mean range of motions was 74.1° (range, 50° to 90°) for abduction, 65.8° (range, 40° to 90°) for external rotation at 90 degrees of abduction, and 118.3° (range, 70° to 160°) for forward flexion at one year postoperatively. The mean Constant score was at the final follow-up was 76.4±8.7 (range, 63 to 90). Outcomes of patients are shown in **Table 2.**

Complications developed in 2 patients. Screw cut-out was seen in patient 2 at 6 months after surgery, without loss of alignment and collapse. Only involved screw was removed. In patient 12, avascular necrosis developed and conversion to reverse shoulder arthroplasty was performed. Other complications including deep or superficial infection, axillary nerve damage or traction related complications were not observed in any of remaining patients.

DISCUSSION

In this study, we describe a new patient positioning technique for the proximal humerus fractures. The lateral decubitus position under traction is a safe and effective method with satisfactory clinical and radiological results.

The importance of anatomical reduction after PHFs have been emphasized in recent studies (5). Bouliane et al. (8) reported that patients achieving simultaneous shaft impaction, shaft medialization, calcar reduction, and neutral neck-shaft angle would be less likely to lose reduction even if the absence of the calcar screw. Dheenadhayalan et al. (6) described the radiographic signs of poor outcomes in PHFs as a terrible triad: neck-shaft angle less than 120 degrees, superior displacement of tuberculum majus, and medial gap of more than 4 mm. Hence, the success or failure of PHFs is deeply rooted in the anatomical reduction quality. If the inherently bone to bone stable fracture configuration does not achieve, the fixation points weaken over time and fixation failure may occur. Therefore, we aimed to improve the reduction quality using a traction in lateral decubitus position. Benefits of this technique include facilitating the anatomical reduction, providing the sagittal alignment directly, eliminating the need for manual reduction

Table 2. Surgical, radiological and clinical outcomes of patients at one year postoperatively

Case	Age/sex	Neer type	Operation time (min)	Radiation exposure time (s)	Union time (wk)	Neck shaft angle (°)	Range of motions (°)			Constant score	Follow-up time (mo)	Complications
							Abduction	External rotation	Forward flexion			
1	54/M	4-part	75	9,1	16	132	60	60	140	70	24	None
2	63/F	3-part	46	4,5	16	136	70	50	130	68	22	Screw Cut-out (Screw Removed)
3	32/F	2-part	55	5,6	12	130	90	70	150	90	22	None
4	69/M	3-part	62	7,1	20	135	60	50	90	63	20	None
5	58/M	4-part	92	14,2	12	124	70	60	100	68	18	None
6	60/F	3-part	58	4,5	8	138	80	80	140	72	17	None
7	55/F	3-part	50	3,8	16	142	90	90	160	82	17	None
8	63/F	4-part	82	6,4	20	136	70	70	120	76	16	None
9	48/F	3-part	45	5,8	12	140	90	70	150	88	14	None
10	72/M	2-part	62	4,1	16	134	90	70	70	86	14	None
11	62/M	3-part	58	4,7	16	139	70	80	100	74	13	None
12	68/F	2-part	44	3,3	12	143	50	40	70	80	12	Avascular necrosis (Converted to RTSA)

RTSA: reverse total shoulder arthroplasty

maneuvers, performing the procedure either alone or with only one assistant. Calcar continuity was achieved in all patients and the mean neck-shaft angle after the union was observed 134.5±3.4 degrees in the present study.

The optimal surgical access for the PHFs is another relevant controversy of the current literature (9-13). The commonly used approach is the classic deltopectoral approach. This method is safe and well known, and this can be extended without risk to the damage of the axillary nerve; however, it limits posterior visualization, especially in presence of displaced greater tuberosity fracture (9). Conversely, the deltoid-split approach provides a direct visualization of the plating zone with minimal soft tissue dissection (14). However, the iatrogenic injury to the axillary nerve is remains a concern (15). Previous studies showed that both deltopectoral and deltoid-split approaches had similar functional results (10,16). On the other hand, Xie et al. (10) reported that the deltoid split approach resulted in a shorter operation time than the deltopectoral approach in their meta-analysis.

Shortening the operating time and avoiding the radiation-related complications are essential but are not the goal of surgery. While there is no limit to operating time or radiation exposure time, these times should be as low as reasonably achievable (17). Many studies reported that the deltoid split approach resulted in a shorter operating time than the deltopectoral approach. (10) On the other hand, the deltopectoral approach had advantage of less radiation exposure time (16). According to the outcomes of the present study, the operating time and the radiation exposure time in our technique are better than both deltoid-split and deltopectoral techniques in supine or beech chair positions when compared with previous studies (**Table 3**) (16,18). The mean operating time was 60.7±15.2 min, and the mean radiation exposure time was 6.1±3.0 s in the present study.

Several studies examined the effects of shoulder movements on axillary nerve position. Cheung et al. (19) reported the shoulder abduction has to greatest effect on the distance of the axillary nerve to acromion. They recommended splitting the deltoid no more than 5 cm distal to the acromion in order to prevent the axillary nerve damage. Moreover, increasing shoulder abduction would increase the strain of the axillary nerve, and it should be kept in mind during the deltoid-split approach. In our study, the shoulder was secured at 30 degrees of abduction. On the other hand, the effect of the calcar screws on the fracture stability has been emphasized in most studies (20). Furthermore, some authors recommended avoiding calcar screws in terms of the risk of axillary nerve damage (21). However, Shin et al. (22) reported that the modified deltoid split approach with axillary nerve mobilization yielded excellent outcomes. They showed no patients had sensory or motor deficits in the axillary nerve with their technique. Traver et al. (23) also showed that prolonged soft tissue retraction may led to the risk of axillary nerve damage. In the present study, no axillary nerve damage was observed in any of the patients. These results support that the described technique is a successful method in selected patients with PHFs.

Some issues need to be mentioned for the present method. The lateral decubitus positioning technique decreases the working area for the surgeon due to medially and laterally positioning of the C-arm. In addition, the described technique via deltoid-split approach might not be a solution for advanced PHF types such as head splitting or fracture dislocations. However, the deltopectoral approach can also be considered as an alternative option for these cases (24).

Table 3. Recent studies on surgical treatment of proximal humerus fractures

Authors, year	N	Mean age, year	Neer classification (1-/2-/3-/4-part)	Patient position	Approach	Operation time, min, mean±SD (range)	Radiation exposure time, s, mean±SD (range)	Follow-up month (range)	Constant score	Complications
Buchmann[25], 2021	149	64.84	NA	NA	DP	121.33±52.5)	191.1	12	NA	15
	49	63.86	NA	NA	MIO-DS	108.02±43.3	181.4	12	NA	1
Rouleau[9], 2020	41	62	0/21/14/2	NA	DP	96±34	NA	28±18	NA	7
	44	63	0/20/20/0	NA	MIO-DS	92±33	NA	25±12	NA	12
Borer[14], 2020	23	62	0/7/11/5	Beach-chair	DP	102 (77-115)	NA	62 (43-88)	82	5
	39	67	0/11/23/5	Beach-chair	MIO-DS	85 (75-112)	NA	41 (24-54)	79	5
Wang[18], 2020	51	62.02	0/16/21/12	Beach-chair	DP	62.94±10.18	4.37±0.72	16.04	86.49	2
	64	62.09	0/18/30/16	Beach-chair	MIO-DS	82.25±12.36	7.27±0.93	16.25	83.75	3
Kim[16], 2019	17	52.6	0/17/0/0	Supine	DP	145.9 (136-154)	1.59 (0.5-2.4)	24	78.4	0
	19	58.7	0/17/0/0	Supine	MIO-DS	109.7 (98-120)	38.5 (32.2-45.7)	24	75.6	0
Zhao[11], 2017	19	63.6	0/7/12/0	Beach-chair	DP	61.4±7.0	NA	10 (4-24)	86.9	3
	17	64.3	0/8/9/0	Beach-chair	MIO-DS	53.6±7.3	NA	10 (4-24)	88.8	2
Buecking[13], 2014	60	67	0/15/46	Beach-chair	DP	67 (61-74)	96 (72-120)	12	73	7
	60	69	0/15/46	Beach-chair	MIO-DS	62 (57-67)	120 (96-144)	12	81	8
Acklin[12], 2013	96	62	NA	Beach-chair	MIO-DS	73±37	108±121	18±6	75	15

DP: deltopectoral; MIO-DS: minimally invasive osteosynthesis-deltoid splitting; SD: standard deviation; NA: not available; Complications: Cut-out/ Nonunion/ Fixation Failure/ Avascular Necrosis/ Loss of Reduction/ Nerve Injury

The study has several limitations. The small sample size is a major limitation which might under-covered some of the outcomes. Although we have reported the preliminary results, the larger cohorts would provide more reliable information. In addition, electromyography or nerve conduction tests for objective evaluation were also not performed to analyze axillary nerve condition with more detail. Nevertheless, we believe that our study provides valuable contribution about plate osteosynthesis for PHFs.

CONCLUSION

Patient positioning in the lateral decubitus position under traction can be considered as a safe, reliable, and reproducible method in selected patients with PHFs. It provides good to excellent clinical outcomes in the early period, facilitates the anatomical reduction. However, further prospective comparative studies are needed to make definitive conclusions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 18.05.2022, Decision No: 2022/240).

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

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare 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. Jawa A, Burnikel D. Treatment of proximal humeral fractures: a critical analysis review. JBJS Rev 2016; 4.
2. Omid R, Trasolini NA, Stone MA, Namdari S. Principles of locking plate fixation of proximal humerus fractures. J Am Acad Orthop Surg 2021; 29: e523-e35.
3. Buyukkuscu MO, Kulduk A, Misir A, Cetinkaya E, Camurcu IY, Gursu SS. Effect of surgical approaches on deltoid innervation and clinical outcomes in the treatment of proximal humeral fractures. Jt Dis Relat Surg 2020; 31: 515-22.
4. Flierl MA, Stahel PF, Hak DJ, Morgan SJ, Smith WR. Traction table-related complications in orthopaedic surgery. J Am Acad Orthop Surg 2010; 18: 668-75.
5. Min KS, Sheridan B, Waryasz GR, et al. Predicting reoperation after operative treatment of proximal humerus fractures. Eur J Orthop Surg Traumatol 2021; 31: 1105-12.
6. Dheenadhayalan J, Prasad VD, Devendra A, Rajasekaran S. Correlation of radiological parameters to functional outcome in complex proximal humerus fracture fixation: A study of 127 cases. J Orthop Surg (Hong Kong) 2019; 27: 2309499019848166.
7. Neer CS, 2nd. Displaced proximal humeral fractures. I. Classification and evaluation. J Bone Joint Surg Am 1970; 52: 1077-89.
8. Bouliane M, Silveira A, AlEidan A, et al. Factors associated with maintaining reduction following locking plate fixation of proximal humerus fractures: a population-based retrospective cohort study. JSES Int 2020; 4: 724-9.
9. Rouleau DM, Balg F, Benoit B, et al. Deltopectoral vs. deltoid split approach for proximal humerus fracture fixation with locking plate: a prospective randomized study (HURA). J Shoulder Elbow Surg 2020; 29: 2190-9.
10. Xie L, Zhang Y, Chen C, Zheng W, Chen H, Cai L. Deltoid-split approach versus deltopectoral approach for proximal humerus fractures: a systematic review and meta-analysis. Orthop Traumatol Surg Res 2019; 105: 307-16.
11. Zhao L, Yang P, Zhu L, Chen AM. Minimal invasive percutaneous plate osteosynthesis (MIPPO) through deltoid-pectoralis approach for the treatment of elderly proximal humeral fractures. BMC Musculoskelet Disord 2017; 18: 187.
12. Acklin YP, Stoffel K, Sommer C. A prospective analysis of the functional and radiological outcomes of minimally invasive plating in proximal humerus fractures. Injury 2013; 44: 456-60.
13. Buecking B, Mohr J, Bockmann B, Zettl R, Ruchholtz S. Deltoid-split or deltopectoral approaches for the treatment of displaced proximal humeral fractures? Clin Orthop Relat Res 2014; 472: 1576-85.
14. Borer J, Schwarz J, Potthast S, et al. Mid-term results of minimally invasive deltoid-split versus standard open deltopectoral approach for PHILOS (proximal humeral internal locking system) osteosynthesis in proximal humeral fractures. Eur J Trauma Emerg Surg 2020; 46: 825-34.
15. Saran N, Bergeron SG, Benoit B, Reindl R, Harvey EJ, Berry GK. Risk of axillary nerve injury during percutaneous proximal humerus locking plate insertion using an external aiming guide. Injury 2010; 41: 1037-40.
16. Kim YG, Park KH, Kim JW, et al. Is minimally invasive plate osteosynthesis superior to open plating for fixation of two-part fracture of the proximal humerus? J Orthop Surg (Hong Kong) 2019; 27: 2309499019836156.
17. Hayda RA, Hsu RY, DePasse JM, Gil JA. Radiation Exposure and Health Risks for Orthopaedic Surgeons. J Am Acad Orthop Surg 2018; 26: 268-77.
18. Wang JQ, Lin CC, Zhao YM, Jiang BJ, Huang XJ. Comparison between minimally invasive deltoid-split and extended deltoid-split approach for proximal humeral fractures: a case-control study. BMC Musculoskelet Disord 2020; 21: 406.
19. Cheung S, Fitzpatrick M, Lee TQ. Effects of shoulder position on axillary nerve positions during the split lateral deltoid approach. J Shoulder Elbow Surg 2009; 18: 748-55.
20. Oppeboen S, Wikeroy AKB, Fuglesang HFS, Dolatowski FC, Randsborg PH. Calcar screws and adequate reduction reduced the risk of fixation failure in proximal humeral fractures treated with a locking plate: 190 patients followed for a mean of 3 years. J Orthop Surg Res 2018; 13: 197.
21. Knezevic J, Mihalj M, Cukelj F, Ivanisevic A. MIPO of proximal humerus fractures through an anterolateral acromial approach. Is the axillary nerve at risk? Injury 2017; 48: 15-20.
22. Shin YH, Lee YH, Choi HS, Kim MB, Pyo SH, Baek GH. A modified deltoid splitting approach with axillary nerve bundle mobilization for proximal humeral fracture fixation. Injury 2017; 48: 2569-74.
23. Traver JL, Guzman MA, Cannada LK, Kaar SG. Is the axillary nerve at risk during a deltoid-splitting approach for proximal humerus fractures? J Orthop Trauma 2016; 30: 240-4.
24. Harun A, Selin E. What should be the surgical position choice in a patient having proximal humeral fracture with developed hypotension? J Orthopedic Surg Techniques 2021; 4.

Original Article

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Using the Charlson comorbidity index as a prognostic factor of lower gastrointestinal system bleeding: the experience of a tertiary center

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ABSTRACT

Introduction: Lesions in the gastroinestinal (GI) tract that are distal to the Treitz ligament are what cause the lower gastrointestinal bleeding (LGB) system. The purpose of this study was to investigate and compare the Charlson Comorbidity Index (CCI), mortality rates, length of hospital stays, need for intensive care, need for blood products, and surgical rates in patients with acute LGB.

Material and Method: Retrospective research was done on patients who had lower GI bleeding and had been seen in our gastroenterology clinic between 2015 and 2021. We looked into the impact of CCI on patients' follow-up after LGB.

Results: The mean age of the 210 patients who had lower GI bleeding was 67.70±13.67 years. For all of the patients, the median CCI value was 4.00. (2.00-5.00). While 16 study participants (group 1) passed away, 194 participants (group 2) were released from the hospital. The variance in the median CCI values between the two groups was statistically significant (p>0.001). The results of a multivariate logistic regression analysis revealed that CCI was a reliable predictor of mortality (p>0.001).

Conclusion: It was found that CCI was an accurate predictor of mortality. CCI ought to be regarded as a crucial factor in the treatment of patients who are bleeding from their lower gastrointestinal tract.

Keywords: Charlson comorbidity index, colonoscopy, lower gastrointestinal bleeding

INTRODUCTION

Although the definition of lower gastrointestinal bleeding (LGB) includes bleeding distal to the ligament of Treitz, it is generally used for bleeding from the anorectal region or colon. Most of patients presenting with LGI bleeding are over 70 years of age (1). Hospitalization rates are lower than those for upper GI bleeding. Patients may present with 'occult bleeding' characterized by the presence of occult blood in the stool, or with cherry-bruised or bright red stools (hematochezia) or black stools (melena). On the other hand, it should not be forgotten that hematochezia may develop in massive upper GI bleedings (2).

Diverticulosis, angiodysplasia, ischemic colitis, infectious or inflammatory bowel disease, or cancer are all possible causes of acute LGI bleeding. Additionally, it might appear following a procedure like polypectomy. Diverticulosis and angiodysplasia hemorrhages are typically massive and painless, whereas bleeding from an inflammatory source is typically accompanied by diarrhea and abdominal pain. Diverticulosis is found in the etiology of 15% to 55% of patients (3,4). Angiodysplasia has been reported as the other most cause of LGI bleeding in patients over 65 years of age (5,6). The hemorrhoids are the most cause of rectal bleeding and usually causes minor bleeding (7). Patients with acute LGI bleeding may have their prognosis affected by clinical findings, age, anticoagulant/antiaggregant use, and the presence of comorbid conditions. Therefore, it must be recognized which patients have a high risk of complications or which patients are suitable for discharge. Charlson Comorbidity Index (CCI) is one of the prediction models to determine high and low-risk patient groups (7).

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CCI was first used to predict prognosis due to comorbid disease in 1887. The following studies also showed that CCI is an important and effective prognostic marker for mortality. CCI is a method that consists of 19 parameters and is applied by categorizing the comorbidities of the patients and scoring them between 1-6 points, providing predictivity in terms of mortality. The higher the CCI score, the higher the mortality observed (8-11).

In this study, we aimed to investigate and compare patients presenting with acute LGI bleeding in terms of the Charlson Comorbidity Index and mortality rates, hospitalization rates and durations, need for intensive care, need for blood products, and rate of going to surgery. Accordingly, it was evaluated whether a prognostic prediction could be made according to the CCI scores at the time of admission to the hospital.

MATERIAL AND METHOD

The study was carried out with the permission of the Ankara City Hospital Scientific Research Evaluation and Ethics Committee (Date:16.09.2019, Decision No: E1-22-2327). We obtained an informed consent form from all patients for colonoscopy. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Retrospective analysis was performed on patients who were hospitalized after being admitted to the emergency room with LGI bleeding between January 2015 and August 2021. The patient files and hospital automation system were used to gather information about the patients' demographics, comorbid disease histories, and drug use histories. The length of the patients' hospital stays and, if any, their time in the intensive care unit (ICU) were assessed. It was noted whether the patients received fresh frozen plasma (FFP) or erythrocyte suspension (ES).

All patients underwent colonoscopies using colonoscopes with the models CF-Q150L and CF-H170L made by Olympus. All patients had their anal examinations and rectal touches evaluated prior to the procedure. Before the procedure, each patient was prepared for colonoscopy with oral colonoscopy solution and 2 intermittent enemas.

The patients' colonoscopy results were documented. Patients who underwent colonoscopic intervention but still experienced bleeding who were referred for surgery were noted. CCI of all patients were calculated by analyzing the medical information of the patients (**Figure 1**). Total scores were calculated and recorded for patients.

Charlson comorbidity indexes (CCI) Scoring	
Comorbidity	**Score**
Myocardial ınfarction (MI)	1
Congestive heart failure (CHF)	1
Peripheral vascular disease	1
Cerebrovascular disease or transient ıschemic attack	1
Hemiplegia	2
Renal disease	2
Mild liver disease	1
Severe liver disease	3
Diabetes mellitus (DM)	1
Complicated diabetes	2
Peptic ulcer	1
Leukemia	2
Lymphoma	2
Solid tumor	2
Metastatic solid tumor	6
Dementia	1
Chronic pulmonary disease	1
Hıv/aıds	6
Rheumatological disease	1

Figure 1. Charlson Comorbidity Index

As the primary outcomes of the study, it has been aimed to determine the relationship between the CCI scores calculated at the time of admission to the hospital and the rates of hospitalization, hospitalization in the intensive care unit, and mortality. The variables of the study are the comorbidities of the patients used when calculating the CCI scores. According to the CCI scoring system, each comorbidity has a specific score and these scores were calculated.

All patients who were hospitalized with lower GI bleeding within the predetermined time frame and were admitted to the emergency room were included in the study without using any particular sampling methodology.

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

We reviewed the patients' demographic and clinical details, colonoscopy results, duration of hospital and intensive care stay, and CCI. The distribution patterns of the continuous variables were investigated using the Kolmogorov-Smirnov test. Gender, antiaggregant and anticoagulant use, surgery, colonoscopy results, and ICU hospitalization were analyzed between the two groups using the $\chi 2$ -test or Fisher's exact test. Continuous variables were analyzed with the Mann-Whitney U test if they had an abnormal distribution pattern or with the Student's t-test if they had a normal distribution pattern. The correlation between CCI and duration of hospital and intensive care stay was evaluated using Spearman's test. To determine the independent predictors of mortality, univariate and

multivariate logistic regression analyses were performed. The capacity of CCI value in predicting the presence of mortality was analyzed using receiver operating characteristic (ROC) curve analysis. Kaplan-Meier curves were constructed to compare survival between groups and the log-rank test was used to determine significance. A value of p <0.05 was considered statistically significant. The IBM Statistical Package for the Social Sciences for Windows, version 25.0, IBM.Corp., Armonk, NY, 2012 was used for the statistical analysis.

RESULTS

One hundred two (49%) of the 210 patients included were male in the study. The patients mean age was 67.70±13.67. Colonoscopy was performed in all patients. In **Table 1**, the results of colonoscopy are listed. The median length of hospital stay was 9.00 (5.00-15.00) days. While 49% of all patients were admitted to the ICU, the median length of ICU stay was 0 (0-5.00) days. In addition, the median CCI value of all patients was 4.00 (2.00-5.00). While 16 of the patients (group 1, 8%) included in the study died, the others (group 2, n=194, 94%) were discharged from the hospital. While the mean age of the patients in group 1 was 72.25±14.09 years, it was 67.33±13.61 years in group 2. There was no statistical significance between the two groups in terms of gender (male; group 1, n=5 (31%) vs. group 2, n=97 (50%); p=0.15), antiaggregant and anticoagulant use. Length of hospital stay (21.00 (9.75-34.25) vs. 8.00 (4.00-15.00); p= 0.001), intensive care hospitalization rates (12 (75%) vs. 90 (46%); p= 0.03) and length of ICU stay (14.00 (1.25-21.50) vs. 0 (0-4.00); p= <0.001) were higher in group 1. The median CCI values between the two groups (group 1 vs. group 2; 8.00 (7.00-9.75) vs. 2, 3.00 (2.00-4.00), p=<0.001; respectively) were statistically significantly different (**Table 1**).

We performed logistic regression analyses to determine the independent predictors of mortality. In multivariate logistic regression analysis, CCI (OR:4.511, 95% CI: 2.128-9.564, P<0.001) was identified as an independent predictor of mortality (**Table 2**). **Figure 2** presents Kaplan-Meier survival curves when patients were divided according to CCI value. Patients with CCI <7 had significantly better survival when compared with patients with CCI≥7 (Log rank P<0.001). In the ROC analysis (**Figure 3**) of mortality prediction, the AUC value of CCI was determined as 0.931 (95% CI: 0.853-0.999, p<0.001). At the cut-off value of 6.5, CCI had sensitivity, specificity, positive predictive and negative predictive values of 87.5%, 93.8 %, 53.8%, 98.9% respectively.

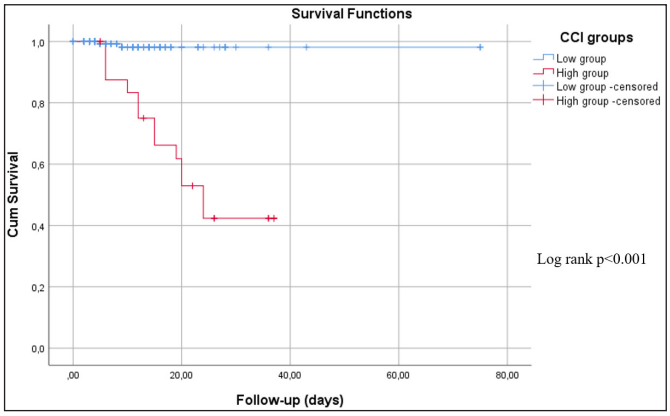

Figure 2. Kaplan-Meier survival curves of CCI subgroups.
CCI: Charlson Comorbidity Index

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

	Total (n=210)	Group 1 (n=16)	Group 2 (n=194)	P
Age, years	67.70±13.67	72.25±14.09	67.33±13.61	0.17
Gender, male, n (%)	102 (49)	5 (31)	97 (50)	0.15
Antiaggregant, n (%)	78 (37)	6 (38)	72 (37)	0.98
Anticoagulant, n (%)	58 (27)	3 (19)	55 (28)	0.41
Surgery, n (%)	20 (10)	5 (31)	15 (8)	0.01
Colonoscopy				
Angiodysplasia, n (%)	52 (25)	0 (0)	52 (27)	0.017
Malignancy, n (%)	17 (8)	3 (19)	14 (7)	0.13
Polyp, n (%)	21 (10)	0 (0)	21 (11)	0.38
Diverticulum, n (%)	64 (31)	4 (25)	60 (31)	0.62
Hemorrhoids, n (%)	12 (6)	0 (0)	12 (6)	0.61
Ischemic colitis, n (%)	38 (18)	7 (44)	31 (16)	0.006
Inflammatory bowel disease, n (%)	4 (2)	0 (0)	4 (2)	1.0
Dieulafoy, n (%)	2 (1)	2 (13)	0 (0)	0.005
Length of hospital stay, day	9.00 (5.00-15.00)	21.00 (9.75-34.25)	8.00 (4.00-15.00)	0.001
Intensive care hospitalization, n (%)	102 (49)	12 (75)	90 (46)	0.03
Length of ICU stay, day	0 (0-5.00)	14.00 (1.25-21.50)	0 (0-4.00)	<0.001
ES replacement, units	3.00 (1.00-6.00)	7.00 (6.00-10.25)	3.00 (1.00-6.00)	<0.001
FFP replacement, units	0 (0-0)	0 (0-0)	0 (0-0)	0.06
CCI	4.00 (2.00-5.00)	8.00 (7.00-9.75)	3.00 (2.00-4.00)	<0.001

ICU: Intensive care unit, ES: Erythrocyte suspension, FFP: Fresh frozen plasma, CCI: Charlson Comorbidity Index. Statistically significant results (p<0.05) were shown in bold type.

Table 2. Univariate and multivariate logistic regression analysis shows the independent predictors of mortality

	Univariate				Multivariate			
	OR	95% CI		P	OR	95% CI		P
		Lower	Upper			Lower	Upper	
Age, years	1.028	0.988	1.070	0.170				
Gender, male	0.455	0.152	1.357	0.158				
Surgery	5.424	1.665	17.673	0.005	1.036	0.113	9.458	0.975
Angiodysplasia	0.000	0.000	-	0.997				
Ulcer	4.090	1.417	11.801	0.009	20.208	1.816	224.830	0.014
Dieulafoy	0.000	0.000	-	0.999				
Duration of hospital stay	1.054	1.017	1.093	0.004	0.917	0.816	1.030	0.145
Intensive care	3.467	1.080	11.128	0.037	0.182	0.019	1.739	0.139
ES replacement	1.187	1.065	1.322	0.002	1.292	1.008	1.657	0.043
CCI	2.973	1.956	4.518	<0.001	4.511	2.128	9.564	<0.001

ES: Erythrocyte suspension, CCI: Charlson Comorbidity Index.

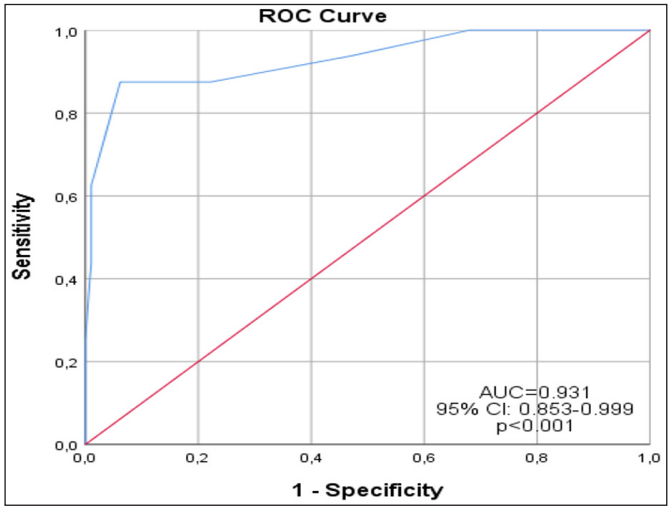

Figure 3. Receiver operating characteristic (ROC) curve for Charlson Comorbidity Index as a predictor of mortality.

The scatter plot in **Figure 4** and **Figure 5** shows the correlation between CCI and length of hospital and ICU stay in the study population. There was a weak correlation between them (Rho=0.252, p<0.001 for hospital stay, Rho=0.273, p<0.001 for ICU stay) (**Table 3**).

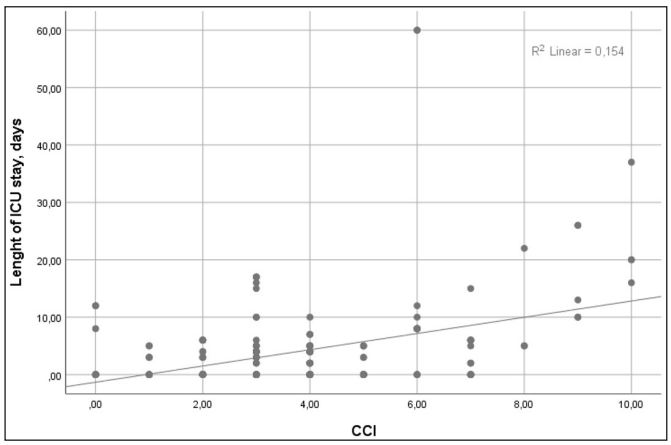

Figure 4. Scatter plot showing a positive linear correlation between length of ICU stay and CCI.
CCI: Charlson Comorbidity Index

Table 3. Correlation Between CCI and length of hospital and ICU stay

	Spearman's Rho	P
Length of hospital stay	0.252	<0.001
Length of ICU stay	0.273	<0.001

ICU: Intensive care unit, CCI: Charlson Comorbidity Index.

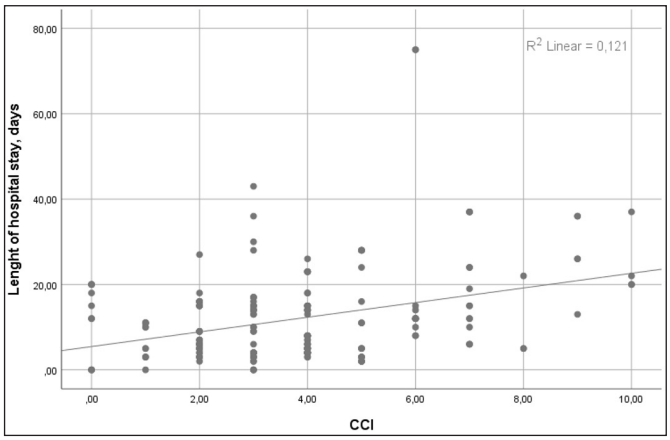

Figure 5. Scatter plot showing a positive linear correlation between length of hospital stay and CCI.
CCI: Charlson Comorbidity Index

DISCUSSION

Hospitalization rates for LGI bleeding range from 33 to 87 per 100,000 people (12). Hospital mortality rates range from 2.5 to 3.9%, and the annual rebleeding rate ranges from 13 to 20% Aoki et al. (13). In our study, 210 patients with LGI bleeding were assessed. While conducting the statistical analysis, the patients were split into two groups. Patients in Group 1 were those who passed away, while those who were released from the hospital were in Group 2. While the median CCI in Group 1 was 8, Group 2 had a median CCI of 3, and the difference between the two was statistically significant. Additionally, the length of hospitalization, the amount of time spent in the intensive care unit, and the requirement for erythrocyte suspension replacement were discovered to be statistically higher

in Group 1 than in Group 2 in the comparative analysis between the two groups. The meta-analysis of Aoki et al.(13) showed that the patients whose CCI score>2 have a higher mortality rate and serious rebleeding risk. Radelli et al. (14) determined that patients with CCI scores ≥3 have a higher mortality rate concerning the results of the study that included 1198 patients from 15 centers (OR 1.20; 95%CI, 1.04-1.38). Strate et al. (15) established in the study that included 252 patients, that the percentage of CCI>2 rates were 49% and 33% in patients with serious bleeding or not, respectively (OR 1.91; 95%CI, 1.15-3.17). They determined that having a CCI>2 is an independent risk factor for LGI bleeding.

The first step in the management of patients with LGI bleeding is to determine the severity of bleeding and risk factors. The most effective treatment is lower gastrointestinal endoscopy (LGE), but there is no consensus on who should is performed emergency LGE (16,18). Gopalswamy et al. (19) looked at 66 patients with GI bleeding who were admitted to the ICU in 2004 and found that patients with high CCI scores had a significantly higher mortality rate. In our study, the group with higher CCI had significantly higher mortality and morbidity, and CCI was also found to be an independent predictor of mortality in multivariate regression analysis. The management of patients who have high CCI must be closely monitored during ICU hospitalization because of high mortality rates. We believed that CCI is an appropriate prognostic indicator to determine whether an urgent colonoscopy is necessary. However, prospective and randomized controlled studies with higher populations are needed.

Camus et al. (20) compared CURE hemostasis prognosis score, ASA score and CCI scores in LGI bleeding, and although ASA score was found to be useful in predicting 30-day mortality, CURE and CCI were not found to be useful. In our study, CCI was found to be significant in predicting mortality, and a CCI cut-off value was determined accordingly. In the present study, a CCI cut-off value of 6.5 was found to be useful in predicting mortality with a sensitivity of 87.5% and specificity of 93.8%.

The most significant limitation of our study is that it was conducted retrospectively, with no comparisons to other scoring systems. One of the most impressive aspects of our research is the in-depth statistical analysis. In this way, data was presented to support the use of CCI as a predictive scoring system for patients with LGI bleeding, including a cut-off value, specificity, sensitivity, positive and negative predictive values. Furthermore, all patients were actively and individually followed up with throughout the process, and data was collected that was completely reliable.

CONCLUSION

In this study, hospitalized patients with LGI had their Charlson Comorbidity Index and mortality rates, hospitalization rates and lengths of stay, needs for intensive care, and needs for blood products compared. As a result, it was assessed to see if a prognostic prediction could be made based on the CCI scores at the time of hospital admission. CCI was also discovered to be a standalone predictor of mortality. Our research yielded specificity, sensitivity, positive and negative predictive values, as well as the cut-off value for CCI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara City Hospital Scientific Research Evaluation and Ethics Committee (Date:16.09.2019, Decision No: E1-22-2327).

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

Referee Evaluation Process: Externally peer-reviewed.

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REFERENCES

1. Kim BS, Li M, Engel BT, et al. Diagnosis of gastrointestinal bleeding: a practical guide for clinicians. World J Gastrointest Pathophysiol 2014; 5: 467-78
2. Zuccaro G. Management of the adult patient with acute lower gastrointestinal bleeding. American College of Gastroenterology. Practice Parameters Committee. Am J Gastroenterol 1998; 93: 1202-08.
3. Zuckerman GR, Prakash C. Acute lower intestinal bleeding. Part II: etiology, therapy, and outcomes. Gastrointest Endosc 1999; 49: 228-38.
4. Strate LL. Lower GI bleeding: epidemiology and diagnosis. Gastroenterol Clin North Am 2005; 34: 643-64.
5. Boley SJ, Sammartano R, Adams A, DiBiase A, Kleinhaus S, Sprayregen S. On the nature and etiology of vascular ectasias of the colon. Degenerative lesions of aging. Gastroenterology 1977; 72: 650-60.
6. Boley SJ, DiBiase A, Brandt LJ, Sammartano RJ. Lower intestinal bleeding in the elderly. Am J Surg 1979; 137-57.
7. Korkis AM, McDougall CJ. Rectal bleeding in patients less than 50 years of age. Dig Dis Sci 1995; 40: 1520-3.
8. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015; 162: W1-73.

9. 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.
10. Gabriel SE, Crowson CS, O'Fallon WM. A comparison of two comorbidity instruments in arthritis. J Clin Epidemiol 1999; 52: 1137-42.
11. Zhang JX, Iwashyna TJ, Christakis NA. The performance of different lookback periods and sources of information for Charlson comorbidity adjustment in Medicare claims. Med Care 1999; 37: 1128-39.
12. Hussain H, Lapin S, Cappell MS. Clinical scoring systems for determining the prognosis of gastrointestinal bleeding. Gastroenterol Clin North Am 2000; 29: 445-64.
13. Aoki T, Hirata Y, Yamada A, Koike K. Initial management for acute lower gastrointestinal bleeding. World J Gastroenterol 2019; 25: 69-84.
14. Radaelli F, Frazzoni L, Repici A, et al. Clinical management and patient outcomes of acute lower gastrointestinal bleeding. A multicenter, prospective, cohort study. Digestive and Liver Disease 2021; 53: 1141-7.
15. Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. Archives of Internal Medicine 2003; 838-43.
16. Manning-Dimmitt LL, Dimmitt SG, Wilson GR. Diagnosis of gastrointestinal bleeding in adults. Am Fam Physician 2005; 71: 1339-46.
17. Lhewa DY, Strate LL. Pros and cons of colonoscopy in management of acute lower gastrointestinal bleeding. World J Gastroenterol 2012; 18: 1185-90.
18. Jensen DM, Machicado GA, Jutabha R, Kovacs TO. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. N Engl J Med 2000; 342: 78-82.
19. Gopalswamy N, Malhotra V, Reddy N, et al. Long-term mortality of patients admitted to the intensive care unit for gastrointestinal bleeding. South Med J 2004; 97: 955-8.
20. Camus M, Jensen DM, Ohning GV, et al. Comparison of three risk scores to predict outcomes of severe lower gastrointestinal bleeding. J Clin Gastroenterol 2016; 50: 52-8.

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M

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Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams & Wilkins; 1998: 1-10.

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Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD/Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

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Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

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