ISSN: 2619-9793 • E-ISSN: 2148-094X

# istanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

VOLUME 25 • ISSUE 1 • February 2024

## Original Articles



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# İstanbul MEDICAL JOURNAL

İSTANBUL TIP DERGİSİ

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**Web:** www.galenos.com.tr
**Publisher Certificate Number:** 14521

**Publication Date:** February 2024
**ISSN:** 2619-9793 **E-ISSN:** 2148-094X
International periodical journal published four times in a year.

istanbulmedicaljournal.org

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## CONTENTS

### Original Articles

İstanbul Med J 2024; 25(1): 1-5
**DOI:** 10.4274/imj.galenos.2023.56956

# Two Consecutive Visits to the Emergency Department: Potential Role of CBC Parameters in COVID-19 Patients Whose PCR Tests Change from Negative to Positive

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## ABSTRACT

**Introduction:** The coronavirus disease-2019 (COVID-19) pandemic is an important health problem worldwide. In this study, we aimed to investigate the relationship between the clinical features and complete blood count (CBC) parameters of COVID-19 patients who were admitted to the emergency department (ED) and whose first polymerase chain reaction (PCR) test was negative and turned positive on the second admission.

**Methods:** The study was designed as a single-center, retrospective, cross-sectional, and observational study. Demographic characteristics, vital signs, complaints, comorbidities, duration of complaints, time between two admissions, and defined CBC parameters in both the first and second admissions were recorded. Positive parameters were recorded in patients whose first PCR test was negative and turned positive and who were admitted to the ED again within ten days. The relationship between the PCR tests and these parameters was investigated.

**Results:** A total of 123 patients were included in the study at the first admission, 89 of them were symptomatic. Of these, in the symptomatic group, body temperature was found higher and peripheral oxygen saturation percentage was found lower. Hypertension was the most common comorbidity, followed by diabetes mellitus and coronary artery disease, respectively. The most common symptom was fever, followed by cough and pain. The median time between the two PCR tests was six days. The leukocyte count, neutrophil count, lymphocyte count, platelet count, and hematocrit decreased on the second admission, whereas the platelet-lymphocyte ratio (PLR) increased.

**Conclusion:** CBC parameters defined in repeated evaluations with suspicion of COVID-19 may support the predictions of a positive test. Regardless of symptoms, the increase in PLR and decrease in leukocyte count, neutrophil count, lymphocyte count, platelet count, and hematocrit should raise suspicion that the COVID-19 test, which was initially negative, may turn positive in the process.

**Keywords:** COVID-19, emergency department, platelet-lymphocyte ratio, polymerase chain reaction

## Introduction

Coronaviruses pose significant threats to humans and animals. Toward the end of 2019, a new coronavirus was pinpointed as the root cause of a pneumonia outbreak in Wuhan, a city in China. Rapid transmission led to an epidemic within China, followed by an increasing number of cases in various countries worldwide. In February 2020, the World Health Organization officially named the illness coronavirus disease-2019 (COVID-19), an abbreviation for "COVID-19" (1). Swiftly collecting and testing appropriate specimens from individuals who meet the suspected case criteria for COVID-19 is a top priority for the clinical management and control of outbreaks. Nevertheless, it is essential to understand that obtaining one or more negative results through polymerase chain reaction (PCR) tests does not definitively rule out the possibility of COVID-19 infection (2).

In the context of a highly sensitive test, negative results should not be solely relied upon to rule out infection, especially when the pretest likelihood of infection is high. It is crucial for clinicians to exercise caution with unexpected negative outcomes. Assessing test sensitivity in individuals who have had contact with confirmed cases and those who are asymptomatic is a pressing concern. Additionally, it is essential to develop methods to estimate the pretest probability of infection for both asymptomatic and symptomatic individuals, enabling the calculation of

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**Cite this article as:** Erdem B, Dikme Ö, Vatan A, Erdem AB, Dikme Özl. Two Consecutive Visits to the Emergency Department: Potential Role of CBC Parameters in COVID-19 Patients Whose PCR Tests Change from Negative to Positive. İstanbul Med J 2024; 25(1): 1-5.

**Received:** 31.10.2023
**Accepted:** 14.12.2023

posttest probabilities following either positive or negative results. While PCR tests used for diagnosing COVID-19 are highly specific, there have been reports of false-negative results (3-6).

Recognizing COVID-19 early is of paramount importance because of its swift transmission and the potential strain it may place on healthcare systems, particularly in cases where patients initially test negative for COVID-19 using PCR tests. Complete blood count (CBC) is a widely available and cost-effective blood test commonly used in emergency departments, even in resource-constrained settings, and is routinely administered. In our study, we aimed to explore the connection between CBC parameters and clinical characteristics among patients who were readmitted to the emergency department with similar symptoms and subsequently tested positive for COVID-19 after initially testing negative in the preceding ten days.

## Methods

The study was designed as a single-center, retrospective, cross-sectional, and observational study. The current study protocol was reviewed and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2581, date: 13.11.2020). The population of the study consisted of patients who were admitted to the ED between 01.04.2020 and 30.05.2020, were evaluated as a pre-diagnosis of COVID-19, and requested PCR test. We included ED patients whose first PCR test was negative and became positive within the next ten days. We excluded patients who were younger than 18 years of age, whose clinical data were missing, and whose CBC parameters and PCR tests could not be studied for technical reasons.

The patient's demographic characteristics, vital parameters, comorbidities, and symptoms on admission were recorded. We recorded leukocyte count, neutrophil count, lymphocyte count, platelet count, hematocrit, immature granulocyte count, and neutrophil percentage from the CBC parameters studied both in the first and second admissions. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) values were calculated. The relationship between defined CBC parameters and PCR tests that became positive and negative at the first admission was investigated.

### Statistical Analysis

Statistical analyses were performed using the SPSS version 22.0 program. The normality of continuous variables was evaluated using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as numbers and percentages. Categorical variables were compared using Fisher's exact test. The Wilcoxon test was used for dependent variables and the Mann-Whitney U test was used for independent variables when examining the changes in non-normally distributed (non-parametric) variables. In the correlation analysis, the p-value and correlation coefficient (r) were given together using the Spearman correlation test. All analyses were performed using a 95% confidence interval. Statistical significance was accepted as $p<0.05$.

## Results

A total of 12,140 patients were retrospectively analyzed for appropriate the International Classification of Diseases-10 diagnoses using the Patient Information Management System between 01.04.2021 and 30.05.2021. Among these patients, one thousand nine hundred and fifty-six patients (16.1%) were excluded because their first PCR tests were positive. Of the remaining 10,184 patients, 3,268 were re-admitted to the ED at least once within 10 days. A total of 2,297 (70.3%) patients did not have a contact history in terms of COVID-19. We identified 971 patients whose first PCR test was negative, who had a second PCR test within ten days, and whose contact status was known. Among these, only 123 patients underwent CBC tests in both admissions (Figure 1). According to the symptom status, the "asymptomatic group" included 34 (27.6%) patients who declared possible contact but had no symptoms on the first admission. "Symptomatic group" included 89 (72.4%) patients who had symptoms possible due to COVID-19 on the first admission and who had a positive second PCR test while the symptoms were still in progress by re-admission. Of the patients, 76 patients (61.8%) were male and 47 patients (38.2%) were female. The median age was 41 years (range: 18-93), and the number of patients ≥65 years was 17 (13.8%). Body heat was higher and peripheral oxygen saturation percentage was lower in the symptomatic group. Hypertension was the most common comorbid disease, followed by diabetes mellitus and coronary artery disease, respectively. The most common symptom was fever, followed by pain and cough. The median times between the two tests were six days (4-7) and six days (5-7), respectively (Table 1). When the difference between the two groups in terms of CBC parameters was investigated, it was observed that on the first admission, the immature granulocyte count and PLR were higher in the symptomatic group than in the

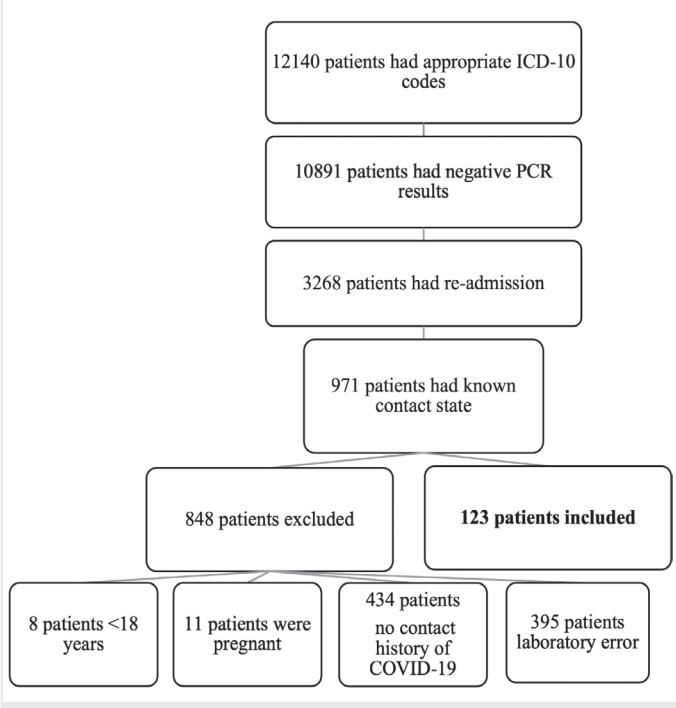


**Figure 1.** Study flowchart
ICD: International Classification of Diseases-10, PCR: Polymerase chain reaction, COVID-19: Coronavirus disease-2019

asymptomatic group, but on the second admission, only the immature granulocyte count was higher in the symptomatic group than in the asymptomatic group, which was statistically significant.

When we examined the CBC parameters of 123 patients regardless of symptoms, leukocyte count, neutrophil count, lymphocyte count, platelet count, and hematocrit decreased, whereas PLR increased at the second admission (Table 2). The immature granulocyte count, neutrophil percentage, and NLR were not statistically significant. Decreases in leukocyte and immature granulocyte counts were not statistically correlated with the asymptomatic group. The statistically correlated parameters in both groups are shown in Table 3. While we found decreases in neutrophil count, lymphocyte count, platelet count, hematocrit, and NLR in both groups, we found increases in neutrophil percentage and PLR. In the symptomatic group, the decrease in leukocytes and neutrophils had a higher correlation coefficient, whereas in the asymptomatic group, the decrease in platelets and hematocrit had a higher correlation coefficient. The obvious correlation was the reduction in the neutrophil count in the symptomatic group (R: 0.768).

## Discussion

COVID-19 is a highly complex disease and a serious health threat worldwide. Overall, COVID-19 resulted in serious economic costs. Thus,

**Table 1. Characteristics of the patients**

| Characteristics | | Symptomatic | Asymptomatic | p |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age | Median (IQR) | 43 (31-57) | 40,5 (33-51) | 0.565* |
| Elderly age (>65 years) | n (%) | 13 (14.6) | 4 (11.8) | 0.467# |
| Male | n (%) | 56 (62.9) | 20 (60.6) | 0.684# |
| Smoker | n (%) | 34 (38.2) | 12 (35.3) | 0.467# |
| **Vital signs** | | | | |
| Systolic blood pressure (mmHg) | Median (IQR) | 130 (124-135) | 135 (125-140) | 0.103* |
| Diastolic blood pressure (mmHg) | Median (IQR) | 75 (70-80) | 75 (70-80) | 0.569* |
| Pulse (/min) | Median (IQR) | 90 (85-100) | 87.5 (81-97) | 0.251* |
| Body temperature (°C) | Median (IQR) | 37 (36.4-37.5) | 36.9 (36.7-37) | **0.023*** |
| $SpO_2$ (%) | Median (IQR) | 96 (94-97) | 98 (96-98) | **<0.001*** |
| **Comorbidities** | | | | |
| Hypertension | n (%) | 20 (22.5) | 6 (17.7) | 0.375# |
| Diabetes mellitus | n (%) | 11 (12.4) | 5 (14.7) | 0.468# |
| Coroner artery disease | n (%) | 10 (11.2) | 4 (11.8) | 0.578# |
| Asthma/COPD | n (%) | 10 (11.2) | 1 (2.4) | 0.136# |
| Malignancy | n (%) | 6 (6.7) | 1 (2.4) | 0.375# |
| Immunosuppression | n (%) | 7 (7.9) | 1 (2.4) | 0.296# |
| **Time** | | | | |
| Contact time (day) | Median (IQR) | 3 (2-4) | 2.5 (2-4) | 0.787* |
| Time between two PCR tests (day) | Median (IQR) | 6 (4-7) | 6 (5-7) | 0.783* |

*Mann-Whitney U test, #Fisher's exact test, COPD: Chronic obstructive pulmonary disease, PCR: Polymerase chain reaction

**Table 2. CBC parameters of patients at the first and second admission**

| CBC parameters | First admission | Second admission | p* | R# | p** |
|---|---|---|---|---|---|
| | Median (IQR) | Median (IQR) | | | |
| Leukocyte | 7.12 (5.73-8.55) | 6.31 (5.07-6.93) | **<0.001** | **0.747** | **<0.001** |
| Neutrophil | 4.47 (3.37-5.36) | 3.54 (2.86-4.32) | **<0.001** | **0.768** | **<0.001** |
| Lymphocyte | 1.80 (1.26-2.37) | 1.38 (1.09-1.80) | **<0.001** | 0.605 | **<0.001** |
| Platelet | 234 (191-282.5) | 214 (186-265.5) | **<0.001** | 0.665 | **<0.001** |
| Hematocrit | 41.9 (36.2-44.9) | 40.1 (35.1-43.4) | **<0.001** | 0.708 | **<0.001** |
| Immature granulocyte | 0.02 (0.01-0.03) | 0.02 (0.01-0.03) | **<0.001** | 0.694 | 0.270 |
| Neutrophil percentage | 62.2 (53.7-69.4) | 63.1 (56.2-68.7) | **<0.001** | 0.485 | 0.218 |
| Neutrophil-lymphocyte ratio | 2.43 (1.57-3.61) | 2.38 (1.74-3.18) | **<0.001** | 0.616 | 0.950 |
| Platelet-lymphocyte ratio | 126.9 (103.5-179.4) | 155.1 (116.3-203.7) | **<0.001** | 0.512 | **<0.001** |

*Spearman correlation, #Linear regression coefficient, **Wilcoxon test, CBC: Complete blood count, IQR: Interquartile range

**Table 3. Comparison of CBC parameters in the first and second admissions of patients by distinguishing between symptomatic and asymptomatic groups**

| CBC parameters | Group | First admission | Second admission | p* | R# | p** |
|---|---|---|---|---|---|---|
| | | Median (IQR) | Median (IQR) | | | |
| Leukocyte | A | 6.87 (5.54-8.51) | 6.07 (5-6.88) | **<0.001** | **0.797** | **<0.001** |
| | B | 7.88 (6.13-8.75) | 6.70 (5.09-7.32) | 0.078 | 0.306 | **<0.001** |
| Neutrophil | A | 4.17 (3.11-5.60) | 3.54 (2.81-4.28) | **<0.001** | **0.801** | **<0.001** |
| | B | 4.61 (3.87-5.47) | 3.54 (3.12-4.53) | **0.046** | 0.345 | **<0.001** |
| Lymphocyte | A | 1.71 (1.25-2.20) | 1.38 (1.08-1.69) | **<0.001** | **0.668** | **<0.001** |
| | B | 2.04 (1.49-2.55) | 1.38 (1.11-1.92) | **0.011** | 0.430 | **<0.001** |
| Platelet | A | 233 (181-281) | 214 (187-273) | **<0.001** | 0.650 | **0.007** |
| | B | 242.5 (193-284) | 214 (185-244) | **<0.001** | **0.740** | **0.001** |
| Hematocrit | A | 41.4 (35.5-45) | 40.1 (34.7-43.4) | **<0.001** | 0.687 | **0.002** |
| | B | 42.2 (38.1-44.8) | 40.1 (36.6-44.1) | **<0.001** | **0.786** | **0.004** |
| Immature granulocyte | A | 0.02 (0.01-0.03) | 0.02 (0.01-0.03) | **<0.001** | 0.606 | 0.681 |
| | B | 0.02 (0.02-0.03) | 0.02 (0.01-0.02) | 0.189 | 0.231 | 0.152 |
| Neutrophil percentage | A | 61.8 (53.2-68.7) | 63.1 (56-68.6) | **<0.001** | 0.448 | 0.400 |
| | B | 62.6 (54.2-71.2) | 63.1 (57.1-69.4) | **<0.001** | 0.614 | 0.288 |
| Neutrophil-lymphocyte ratio | A | 2.43 (1.59-3.69) | 2.38 (1.73-3.19) | **<0.001** | 0.617 | 0.711 |
| | B | 2.41 (1.55-3.45) | 2.44 (1.88-3.16) | **<0.001** | 0.583 | 0.578 |
| Platelet-lymphocyte ratio | A | 129.7 (103.4-196.7) | 155.1 (119.1-205.9) | **<0.001** | 0.530 | **0.002** |
| | B | 121.9 (106.1-148.4) | 147.2 (112.4-176.3) | **0.012** | 0.426 | **0.011** |

A: Symptomatic group. B: Asymptomatic group. *Spearman correlation, #Linear regression coefficient, **Wilcoxon test, CBC: Complete blood count, IQR: Interquartile range

the rapid detection of COVID-19 is crucial to avoid contamination and adverse outcomes and reduce morbidity by properly initiating treatment before irreversible damage occurs. Recent studies reported that the sensitivity and specificity of PCR tests were 80% and 98-99%, respectively (7). Even though a test is highly sensitive, the results cannot rule out infection if the clinical probability is high. Therefore, clinicians should pay attention to unexpected negative results. Early diagnosis of COVID-19 is still difficult today because it is characterized by many clinical manifestations. Thus, it is important to identify a reliable biomarker for screening high-risk patients and candidates for COVID-19. Among all the investigated COVID-19 biomarkers, CBC parameters could represent valuable tools. Indeed, CBC has several advantages. First, it is the most commonly ordered test in all clinical settings, including EDs; second, clinicians order it almost routinely. Especially in terms of limited resources, it is more important to identify early symptomatic or asymptomatic patients whose PCR test is negative at first admission and whose PCR test will probably turn positive in the process. Studies have reported that lymphopenia is more common at first admission. Ferrari et al. (8) reported in a study that COVID-19 patients with positive PCR tests had a lower lymphocyte count on the first admission. We found similar results in terms of lymphocyte count, but the platelet count on admission was lower, unlike in this study. A study by Guan et al. (9) reported thrombocytopenia in approximately one-third of patients. This may be because of the inclusion of asymptomatic patients with a clinically milder infection in our study. Inflammatory biomarkers play an important role in the diagnosis and prognosis prediction of various diseases, including COVID-19. Many publications report that NLR and PLR are associated with diagnosis, clinical course, and outcome because they're reflecting the increased inflammatory process (10-13). In this study, we did not find any relationship with NLR. We think that this may be because symptomatic patients were included in the study at a very early stage and asymptomatic patients. Similarly, Bedel et al. (14) reported that plasma inflammatory biomarkers such as NLR and PLR are time-sensitive and dynamic parameters accompanying the course of the disease, and the time elapsed since the onset of symptoms may affect NLR and PLR. We found that the PLR was higher on the second admission, which was statistically significant. Many studies in the literature have reported that PLR can be used in diagnosing and predicting the prognosis in patients with COVID-19. We found that the PLR was higher on the second admission as statistically significant (15).

### Study Limitations

There are some limitations in this study. Our study was a single-center, retrospective study, and the results cannot be generalized to the population. The sample size is small, and studies with more patients are needed. Finally, the negative results of the PCR tests on the first admission may be false negative. We could not confirm this because we did not perform a second test within 24-48 h.

## Conclusion

In conclusion, repeated CBC tests of suspected COVID-19 patients may predict a positive PCR result on the second admission. Regardless

of symptoms, the increase in PLR and a decrease in leukocyte count, neutrophil count, lymphocyte count, platelet count, and hematocrit should raise suspicion of a COVID-19 test, which was initially negative and may turn positive afterwards.

**Ethics Committee Approval:** The current study protocol was reviewed and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2581, date: 13.11.2020).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Surgical and Medical Practices - B.E., A.B.E., Özl.D.; Concept - B.E., Ö.D., A.V., A.B.E., Özl.D.; Design - B.E., Ö.D., A.V., A.B.E., Özl.D.; Data Collection or Processing - B.E., A.B.E.; Analysis or Interpretation - B.E., Ö.D., A.V., A.B.E., Özl.D.; Literature Search - B.E., Ö.D., A.V., A.B.E., Özl.D.; Writing - B.E., Ö.D., A.V., A.B.E., Özl.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 6-11
**DOI:** 10.4274/imj.galenos.2024.09365

# Relationship of *LEP, LEPR* Variants, and *LEP* Methylation with Multiple Myeloma and Prognosis

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## ABSTRACT

**Introduction:** Leptin (LEP) and LEP receptor (LEPR) play roles in cancer progression. We evaluated *LEP*-2548G/A and *LEPR* 668 A/G variants in patients with multiple myeloma (MM). In addition, the methylation status of CpG sites at 31 and 51 nucleotides (nt) according to the transcription start region of the *LEP* gene was examined.

**Methods:** DNA was extracted from the peripheral blood of study participants who were healthy controls and patients with MM. These variants were analyzed using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The methylation at -31 and -51 nt in the *LEP* was performed using the methylation-specific PCR method. The 2-year progression-free survival (PFS) and 2-year overall survival (OS) were evaluated according to prognostic factors.

**Results:** There was no significant difference in the genotype distributions of LEPR 668A/G and LEP-2548G/A between the control and patient groups ($p>0.05$). We found that -31 and -51 nt regions of the *LEP* gene were unmethylated in the patient group compared with the control group ($p=0.051$ and $p=0.001$, respectively). The -31 nt methylation was unchanged in 15 patients (78.94%). PFS and OS were higher in these patients than in the others. In multivariate analysis, the methylated/unmethylated ratio at -31 nt methylation was associated with a poor prognosis ($p=0.020$).

**Conclusion:** To our knowledge, our study is the first to examine these variants and their methylation status in Turkish patients with MM. Our results showed that *LEP* gene -31 nt unmethylation was associated with PFS and OS. These results need to be confirmed in different ethnic and larger sample groups.

**Keywords:** Multiple myeloma, leptin, leptin receptor, PCR-RFLP, MS-PCR

## Introduction

Multiple myeloma (MM) is a hematological malignancy that occurs when abnormal plasma cells grow uncontrollably and invade the bone marrow (BM) (1). The average age at diagnosis is 60 years old (2). MM accounts for 1% of all malignancies and 10% of all hematological cancers (3). The incidence of MM is highest in the African population, whereas the lowest rates are observed in the Asian and Mediterranean populations (4). Although advancements in MM treatment have raised the 5-year survival rate to almost 50%, MM is still regarded as incurable. Although the exact cause of MM remains unknown, in previous studies, age, male gender, obesity, exposure to ionizing radiation, and a history of monoclonal gammopathy of undetermined significance (MGUS) have been mentioned as risk factors (5). Many studies have shown that genetic factors play an essential role in the etiology of MM. Genetic factors, particularly those pertaining to immune response genes, increase the likelihood of MM development.

Leptin (LEP), a hormone, is primarily produced by white adipose cells in the body. By affecting energy expenditure and food intake, it has a significant effect on maintaining body weight homeostasis (6). In addition, LEP has various other functions in the body, such as influencing insulin resistance, cell proliferation, oxidative stress, cancer cell inflammation, apoptosis, and immune regulation (7). LEP is found in human peripheral blood, cord blood, and BM blood. Various studies have shown that high levels of *LEP* may affect the onset and progression of many malignancies. LEP exerts its biological effect by binding to and activating leptin receptors (LEPR). The *LEP* gene is on chromosome 7q31.3. The leptin receptor

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**Cite this article as:** Oyacı Y, Nursal AF, Serin İ, Pehlivan S, Pehlivan M. Relationship of *LEP, LEPR* Variants, and *LEP* Methylation with Multiple Myeloma and Prognosis. İstanbul Med J 2024; 25(1): 6-11.

**Received:** 30.10.2023
**Accepted:** 07.01.2024

encoded by the *LEPR* gene is a member of the class 1 cytokine receptor family. LEPR plays a role in the pathogenesis of many malignant cancers (8). *In vitro* and *in vivo* studies have demonstrated the critical role of LEP/LEPR signaling in the growth, maturation, and functionality of hematopoietic progenitor cells and mature blood cells (9). The *LEP* and *LEPR* genes have single-nucleotide polymorphisms (SNPs). The variant -2548G/A (rs7799039) is situated in the promoter region of the *LEP* gene, whereas the variant 668A/G (rs1137101) of the *LEPR* gene is located in the exon 6 region of the *LEPR* gene (10).

Based on this information, in this study, we evaluated whether *LEP*-2548G/A and *LEPR* 668 A/G variants cause susceptibility in patients with MM. In addition, the methylation of CpG sites located at -31 and -51 nucleotides (nt) according to the transcription start region of the *LEP* gene was examined.

## Methods

### Study population

Nineteen patients (7 females and 12 males, median age: 60 years) diagnosed with MM were included in the study. Staging was assigned according to the Durie and Salmon and the International Staging System criteria (11). The clinical characteristics and treatment protocols of the patients were examined. The 2-year progression-free survival (PFS) and 2-year overall survival (OS) were evaluated according to prognostic factors. The healthy control group consisted of 93 healthy individuals (49 females, 44 males, median age: 45 years). The control group was selected from volunteers without any malignancies or chronic diseases. All participants received written explanations of the study objectives and methods.

The Local Ethics Committee approved all procedures involving human subjects during this study, which was conducted in accordance with the Declaration of Helsinki's criteria.

The study was approved by the İstanbul University, İstanbul Faculty of Medicine Local Ethical Committee (approval number: 62734, date: 29/05/2020).

### Genotyping

Peripheral blood was used to extract DNA samples from the groups. The *LEP*-2548G/A and *LEPR* 668A/G variants were analyzed using the polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP). The primer sequence used for *LEP*-2548G/A F:5'-TTTCCTGTAATTTTCCCGTGAG-3' and R:5'-AAAGCAAAGACAGGCATA AAAA- 3', the primer sequence for *LEPR* 668A/G was F: 5'-GCCTAATCCAGTATTTTATATCTG-3' R: 5'GCCACTCTTAATACCCCCAGT. HhaI restriction enzyme for *LEP*-2548G/A and MspI enzyme for *LEPR* 668 A/G were used (12,13). *LEP* gene -31 and -51 nt methylation was performed using the methylation-specific PCR (MS-PCR) method previously described by García-Cardona et al. (14).

### Statistical Analysis

SPSS, version 20.0 for Windows (SPSS, Inc., Chicago, IL, USA) was employed to examine all data. Using Pearson's $\chi^2$ analysis, categorical data were evaluated. In addition, the 95% confidence interval (CI) and odds ratio (OR) were computed. OR (95% CI) was age- and sex- adjusted. The log-rank test was used to compare the patient group's 2-year PFS and OS based on prognostic variables. The threshold for statistical significance was set at a p-value of less than 0.05 in all two-tailed analyses.

## Results

*LEP*-2548G/A, *LEPR* 668 A/G variants, and -31 and -51 nt of the *LEP* gene were examined in patients with MM and controls. The clinical characteristics and treatment regimens of the groups are listed in Table 1.

Table 2 summarizes the distributions of genotypes for these variants in groups. *LEP-2548G/A* and *LEPR-668A/G* genotype distributions did not differ significantly between the patient and control groups ($p>0.05$). The methylation status of the -31 and -51 nt regions of the *LEP* gene significantly differed between patients and controls. There was no methylation in the -31 and -51 nt regions of the *LEP* gene in the

**Table 1. Clinical features and treatment regimens of the groups**

| | MM patients, n=19 (%) | Controls, n=93 (%) |
|---|---|---|
| Age (median) | 60 (41-82) | 45 (18-81) |
| **Gender, n (%)** | | |
| Female/male | 7/12 (37/63) | 49/44 (53/47) |
| **Ig subtypes, n (%)** | | |
| k/L | 12/7 (63/37) | |
| G/A | 12/5 (63/26) | |
| Light chain | 11 (58) | |
| **Stage (Salmon-Durie)** | | |
| I-II | 11 (58) | |
| III | 8 (42) | |
| A/B | 15/4 (79/21) | |
| **ECOG** | | |
| >1 | 6 (32) | |
| Hb (gr/dL) | 11 (7.8-17) | |
| Leukocytes (µL) | 7580 (3680-11330) | |
| Platelets ($10^3$/µL) | 178 (71-567) | |
| CRP (mg/dL) | 3.7 (2.2-234) | |
| LDH (IU/L) | 185 (52-902) | |
| Beta 2-microglobulin (mg/L) | 5.4 (1.4-29.4) | |
| Albumin (gr/L) | 3.5 (1.9-4.7) | |
| **Treatment** | | |
| VCD, APBSCT, and LD | 12 (63) | |
| VCD ± LD | 7(37) | |
| OS: 2 years (%) | 61 | |
| PFS: 2 years (%) | 60 | |
| Mortality | 6 (32) | |
| Mean follow-up (month) | 20.5 (5.5-34.2) | |

MM: Multiple myeloma, Ig: Immunoglobulin, ECOG: Eastern Cooperative Oncology Group performance status, Hb: Hemoglobin, CRP: C-reactive protein, LDH: Lactate dehydrogenase, VCD: Bortezomib, cyclophosphamide, and dexamethasone, APSCT: Autologous peripheral blood stem cell transplantation, LD: Lenalidomide and dexamethasone, OS: Overall survival, PFS: Progression-free survival

patient group compared with the control group (p=0.051 and p=0.001, respectively).

The patient group's 2-year PFS and 2-year OS were compared according to prognostic factors. The results are shown in Table 3. The mean 2-year PFS was 22 months, and the mean 2-year OS was 15.2 months. -31 nt methylation was unchanged in 15 patients (78.94%). PFS and OS were higher in these patients than in others (p=0.019 and p=0.048).

In multivariate analysis, the methylated/unmethylated ratio at -31 nt methylation was associated with a poor prognosis (p=0.020) (Table 4).

**Table 2. The genotype distributions of *LEP-2548G/A* and *LEPR-668A/G* and methylation status of the *LEP* gene**

| | MM patients, n=19 (%) | Controls, n=93 (%) | OR Exp (B) | 95% CI | p |
|---|---|---|---|---|---|
| ***LEP*-2548G/A** | | | | | |
| **Genotypes** | | | | | |
| G/G | 9 (47.4) | 35 (37.6) | 1.491& | 0.552-4.028& | 0.450& |
| G/A | 5 (26.3) | 46 (49.5) | 2.406* | 0.679-8.523* | 0.174* |
| A/A | 5 (26.3) | 12 (12.9) | 0.662* | 0.158-2.782* | 0.574* |
| ***LEPR* 668A/G** | | | | | |
| **Genotypes** | | | | | |
| A/A | 8 (42.1) | 60 (64.5) | 0.930* | 0.083-10.467* | 0.953* |
| A/G | 10 (52.6) | 27 (29.0) | 0.360* | 0.032-4.070* | 0.409* |
| G/G | 1 (5.3) | 6 (6.5) | 0.806& | 0.091-7.105& | 0.100& |
| **-31 nt methylation** | | | | | |
| Methylated | 15 (78.9) | 86 (92.5) | 4.734* | 0.995-22.513* | **0.051*** |
| Unmethylated | 4 (21.1) | 7 (7.5) | | | |
| **-51 nt methylation** | | | | | |
| Methylated | 10 (52.6) | 90 (96.8) | 52.246* | 7.103-384.532* | **0.001*** |
| Unmethylated | 9 (47.4) | 3 (3.2) | | | |

*: OR (95% CI) was adjusted by age and sex, &Fisher's exact test, OR: Odds ratio, CI: Confidence interval

**Table 3. Univariate analysis (log-rank test) of prognostic factors in 19 patients with MM**

| | | n | 2-year PFS (%) | Log-rank (p) | 2-year OS (%) | Log-rank (p) |
|---|---|---|---|---|---|---|
| | | 19 | 60 | | 61 | |
| Gender | Female/male | 7/12 | 88/47 | 0.252 | 85/48 | 0.259 |
| Age | <65/≥65 | 12/7 | 51/85 | 0.261 | 47/83 | 0.285 |
| Stage (Salmon-Durie) | II/III | 11/8 | 71/36 | 0.490 | 70/48 | 0.577 |
| | A/B | 15/4 | 60/75 | 0.939 | 60/67 | 0.875 |
| ECOG | ≤1/>1 | 13/6 | 60/67 | 0.937 | 60/67 | 0.903 |
| CRP (mg/L) | <5/≥5 | 3/13 | 80/55 | 0.465 | 80/51 | 0.407 |
| First-line treatment | VCD + APSCT + LD | 12 | 76 | | 76 | |
| | VCD ± LD | 7 | 32 (9 months)* | **0.030** | 34 (15.2 month)* | **0.034** |
| *LEP* 668A/G | A/A | 8 | 56 | | 56 | |
| | A/G | 10 | 65 | | 62 | |
| | G/G | 1 | 100 | 0.836 | 100 | 0.769 |
| *LEP* -2548G/A | A/A | 5 | 100 | | 100 | |
| | G/A | 5 | 60 | | 60 | |
| | G/G | 9 | 56 | 0.294 | 56 | 0.433 |
| -31 nt methylation* | Decreased | 4 | 0 (4.3 month)* | | 0 (14.8 month)* | |
| | No change | 15 | 78 | **0.019** | 76 | **0.048** |
| -51 nt methylation* | Decreased | 7 | 62 | | 63 | |
| | Increased | 3 | 66 | | 66 | |
| | No change | 9 | 66 | 0.876 | 66 | 0.831 |

*After first-line treatment, MM: Multiple myeloma, PFS: Progression-free survival, OS: Overall survival, ECOG: Eastern Cooperative Oncology Group performance status, CRP: C-reactive protein, VCD: Bortezomib, cyclophosphamide, and dexamethasone, APSCT: Autologous peripheral blood stem cell transplantation, LD: Lenalidomide and dexamethasone

**Table 4. Multivariate analysis of patients with MM (cox proportional hazard model backward)**

| | OS | | | PFS | | |
|---|---|---|---|---|---|---|
| | Exp (B) relative risk | 95% CI | p | Exp (B) relative risk | 95% CI | p |
| First-line treatment (APSCT +/-) | 0.154 | 0.125-0.964 | **0.046** | 0.069 | 0.006-0.732 | **0.027** |
| -31 nt methylation (M/UM) | 0.189 | 0.034-1.039 | 0.055 | 0.065 | 0.007-0.651 | **0.020** |

MM: Multiple myeloma, OS: Overall survival, PFS: Progression-free survival, CI: Confidence interval, APSCT: Autologous peripheral stem cell transplantation, M: Methylated, UM: Unmethylated

## Discussion

Epidemiological and family studies have determined that the risk of MM and its precursor disease, MGUS, is associated with genetic predisposition (15). One of the known and confirmed risk factors for MM and MGUS is family history. In first-degree relatives of patients with MM, the risk of MM increases two to four times, and the risk of MGUS increases two to three times (16). The initiation and development of MM are accompanied by genetic alterations, such as chromosomal translocations, and structural variants, such as deletions, duplications, and insertions. Deleterious single-nucleotide variations are also frequently observed. These may result in the progression of the illness and treatment resistance (17). Some SNPs have also been shown to play a role in MM susceptibility.

The primary element of the BM microenvironment is crucial for the emergence and development of MM. The BM adipose tissue, which constitutes 50-70% of the BM volume (18). Adipose tissue functions as an endocrine organ that contributes to the release of certain adipocytokines in addition to serving as a store of energy (19). Some studies have shown that changing levels of adipokines secreted from fat tissue play a role in the development of various types of cancer (20). LEP also plays an important role in energy balance and metabolism functions as well as receptors related to adaptive immunity, angiogenesis, and the hematopoietic process (21). LEP levels increase in people with excess fatty tissue that are at increased risk of cancer. This suggests that LEP may play a role in the development of cancer (22). According to certain research examining LEP's impact on hematological cancers, LEP somewhat promotes myeloma cell line proliferation and lessens chemotherapy-induced myeloma cell line apoptosis (23-25). In a meta-analysis where 1269 MM patients and 2158 controls were evaluated, the circulating LEP levels of MM patients were found to be higher than those of controls (26). Esheba et al. (27) and Alexandrakis et al. (28) also supported these results (29). However, there are also studies showing the opposite (30,31). There are studies relating genetic variants of LEP and LEPR to the susceptibility of various malignant tumors (32). *LEP*-2548G/A and *LEPR* 668A/G are the most studied variants. The *LEP*-2548G/A is close to the specificity protein-1 transcription factor binding site located in the *LEP* promoter region. This variant is thought to affect *LEP* gene transcription and expression as well as LEP synthesis and secretion from adipose tissue (12). *LEPR* 668A/G is located in the leptin-binding region in the extracellular domain of the gene (12). This variant, which disrupts LEP binding to its receptor, results in an A to G substitution in exon 6, nucleotide 668, and codon 223 of the start codon (33). Bieńkiewicz et al. (34) reported that the *LEP*-2548A/G A/G genotype may reduce the risk of endometrial cancer formation, whereas the A allele may be a risk factor. The LEP-2548A/G polymorphism was linked to an increased overall risk of cancer, according to a meta-analysis (35). A meta-analysis suggested that *LEPR* 668G/A may play a role in the development of breast cancer in East Asians (36). In addition, it was reported that the *LEPR* 668G/A G/G genotype was related to an increased LEP profile among obese breast cancer females (33). Another study found that *LEPR* 668G/A was not associated with cancer in a study of 35,936 subjects in 44 case-control studies (37). There are not many studies examining these variants in hematological malignancies. These two variants are associated with non-Hodgkin lymphoma (38). Lin et al. (39) showed the same result for *LEP*-2548G/A (39).

In this study, we aimed to investigate whether the *LEP*-2548A and *LEPR*-668G/A variants predispose to the development of MM. DNA methylation pattern is an epigenetic change that affects gene expression. Therefore, we also examined the *LEP*-31 and -51 nt methylation status of the *LEP* gene. We found that *LEP-2548G/A* and *LEPR 668A/G* genotype distributions were not associated with MM development. We found that -31 and -51 nt regions of the *LEP* gene were unmethylated in the patient group compared with the control group. In multivariate analysis, we found that the methylated/unmethylated ratio at -31 nt methylation was related to a poor prognosis.

### Study Limitations

This study has several limitations. First, the sample group was small. Additionally, only two variants in this pathway were evaluated. Other variants in these genes may also play a role in the development of MM. However, it is also an advantage of the study that *LEP*-2548G/A and *LEPR* 668A/G variants and the methylation status of -31 and -51 nt in the *LEP* gene are examined for the first time.

## Conclusion

To the best of our knowledge, this is the first study to assess these variations and the methylation status of this region in Turkish individuals with MM. Although the current study's findings suggest that *LEP* and *LEPR* polymorphisms could not be a risk factor for the onset of MM, further research is necessary to validate and expand on these findings in larger populations and other ethnic groups.

**Acknowledgments:** We respectfully remember all the colleagues we lost in the fight against COVID-19.

**Ethics Committee Approval:** The study was approved by the İstanbul University, İstanbul Faculty of Medicine Local Ethical Committee (approval number: 62734, date: 29/05/2020).

**Informed Consent:** It wasn't obtained.

**Authorship Contributions:** Concept - Y.O., A.F.N., İ.S., S.P., M.P.; Data Collection or Processing - Y.O., A.F.N., İ.S., S.P., M.P.; Analysis or Interpretation - Y.O., A.F.N., İ.S., S.P., M.P.; Literature Search - Y.O., A.F.N., İ.S., S.P., M.P.; Writing - Y.O., A.F.N., İ.S., S.P., M.P.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 12-20
**DOI:** 10.4274/imj.galenos.2024.44420

# Investigation of the Relationship between COVID-19-Induced Dysfunctional Anxiety and Health Literacy in Oncology Patients

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## ABSTRACT

**Introduction:** Improvement of health literacy plays a primary role in improving individual and public health. This study aimed to investigate the relationship between coronavirus disease-2019 (COVID-19)-induced dysfunctional anxiety and health literacy in oncology patients and the factors affecting this relationship.

**Methods:** This study has a descriptive, correlational, and cross-sectional design. Data were collected using a Personal Information Form, Turkey Health Literacy Scale, and Coronavirus Anxiety Scale-Short Form (CAS-SF).

**Results:** The mean age of the patients was 60.68±13.04; their mean total health literacy score was 26.73±12.44; the mean coronavirus anxiety score was 0.98±1.99. There was no significant correlation between the health literacy score and the CAS score ($p>0.05$). There was a significant negative correlation between health literacy and age ($p<0.001$). There was a statistically significant difference between the presence of comorbidities and educational status, and health literacy ($p<0.05$).

**Conclusion:** Because cancer patients with limited levels of health literacy may disrupt their treatment plans in stressful conditions such as pandemics, patients' levels of health literacy should be primarily determined when considering their treatment needs and overall care to ensure that this continues effectively. Training materials and contents should be prepared by considering the patient's age, education level, and comorbidities, as well as the general characteristics of the factor causing the pandemic.

**Keywords:** COVID-19, health literacy, dysfunctional anxiety, nursing, oncology

## Introduction

One in every 4-5 people is diagnosed with cancer in Turkey and all over the world (1). The change in priorities in terms of treatment and diagnosis in hospitals during the coronavirus disease-2019 (COVID-19) process and the rapid increase in the hospital occupancy rate caused delays in the diagnosis and treatment of cancer. This also caused difficulties in determining the incidence and mortality rates of cancer (2). Moreover, patients experienced stress, anxiety, and concerns because all hospitals had to allocate most of their capacity to COVID-19 cases during the pandemic process, the lack of treatment protocols for cancer patients in the early stages of the pandemic, the uncertainties about patient prioritization and the scope of treatment, and the various risks to be encountered if the treatment is delayed or is unable to continue (3). The recognition of COVID-19 as a pandemic, difficulties in its treatment, rate of transmission, and the severe and deadly disease process have caused panic all over the world. Increased COVID-19 cases and death rates reported in the media, pandemic measures, and unfounded news in the press and social media have led to an increase in fear, panic, anger, the feeling of uncertainty, depression, anxiety, loneliness, and even post-traumatic stress disorder in those who had the disease (4-8). Although cancer patients are used to hygiene rules in cancer treatment, the change in the diagnosis and treatment priorities of the health system during the pandemic, as well as the anxiety and concerns regarding having COVID-19 during treatment and infecting their loved ones, have raised the rates of loneliness and depression by 4.5 times (9). According to a comparison between cancer patients and other patient groups coming to medical examinations, the reason for cancer patients taking stricter protective measures in handwashing and compliance with social distance rules is the fear of getting COVID-19 (with the associated impact on their disease and treatment) and the subjective level of knowledge about COVID-19 (10).

Patients' reluctance to attend official health institutions at the beginning of the pandemic, social distance rules, and the call of social media and health institutions not to attend hospitals unless necessary have led

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**Cite this article as:** Topbaş E, Doğan E. Investigation of the Relationship between COVID-19-Induced Dysfunctional Anxiety and Health Literacy in Oncology Patients. İstanbul Med J 2024; 25(1): 12-20.

**Received:** 21.12.2023
**Accepted:** 19.01.2024

patients to prefer social media as a source of information (11). Experiencing the pandemic for the first time has caused confusion with the constantly and rapidly changing flow of information on the spread and course of the virus. The internet has been the most commonly used method to search for and access information on COVID-19 (12,13). However, a large portion of internet users may not have the skills to assess the quality and reliability of health information themselves (14). Due to this rapid flow of information, the pandemic has also created an "infodemic", in which such huge volumes of widely spreading information create much that can be false or misleading, making it difficult to determine what is accurate and what is not. Worldwide health literacy is necessary to resist the indemic and allow individuals to trust and act on reliable information and recommendations (14). If the individual can access basic health information by choosing reliable sources and can interpret and use it, it can be said that the one has health literacy (15). The Centers for Disease Control and Prevention (16) aimed to include organizations, professionals, policymakers, individuals, families, and communities in the national plan of action for health literacy development. Training materials, posters, infographics, social media, media organizations, individual counseling services, and educational institutions are used to improve health literacy. Improvement of health literacy plays a primary role in improving individual and public health.

It has been reported that the level of health literacy is low in seven out of 10 people in the general population in Turkey and that the incidence of chronic diseases increases as health literacy decreases (17). In addition, in our country and worldwide, cancer is the second leading cause of death after cardiovascular diseases. One out of every six deaths globally and one out of every five deaths in our country is due to cancer. Insufficient levels of health literacy also cause disruptions in preventive health services. Individuals with insufficient levels of health literacy are less likely to apply to cancer screening programs, leading to negative consequences in terms of both the improvement of an individual and social health, as well as increased costs (18). Therefore, the aim of this study was to examine the relationship between dysfunctional anxiety, which develops during the pandemic process due to the increasing number of cancer cases and the rapid spread of COVID-19, and health literacy throughout Turkey, along with the factors that affect this relationship. Dysfunctional anxiety is defined as anxiety to which we cannot respond accurately or interpret effectively. It is thought that this study will contribute to this field as no similar studies have been found in the literature so far.

## Methods

### Research Type

This study has a descriptive, correlational, and cross-sectional design.

### Research Place and Time

The study was conducted with patients who applied to the oncology outpatient clinic and chemotherapy unit of Amasya University Sabuncuoğlu Şerefeddin Training and Research Hospital between July 10, 2020 and November 01, 2021. The first normalization process of the COVID-19 pandemic started on January 06, 2020 in Turkey. This new period is called "restricted socialization."

### Research Population and Sample

Considering a correlation of 0.352 between the worry and anxiety scores of patients with diabetes mellitus and the health literacy mean scores of adults in the study conducted by Beyoğlu and Avcı (19), we planned to include 82 cases with a confidence interval of 95% (1-$\alpha$), a test power of 95% (1-$\beta$), and an effect size of $\rho$=0.352. Considering possible data losses and survey errors, the study was completed with 100 patients. Patients aged over 18 years, who were at least primary school graduates, who had no previously diagnosed psychiatric problems, and who were willing to participate in the study were included.

### Data Collection Method

Data were collected using a "Personal Information Form", the "Turkey Health Literacy Scale-32 (THLS-32)" and the "Coronavirus Anxiety Scale-Short Form (CAS-SF)." Questionnaires were completed in 10-15 minutes in one-on-one interviews.

### Data Collection Tools

**Personal Information Form:** This form consisted of 25 questions regarding the socio-demographic, disease-related, and COVID-19-related characteristics of the participants.

**Coronavirus Anxiety Scale-Short Form (CAS-SF):** This scale was developed by Lee (20) as a brief mental health screening tool to identify possible cases of COVID-19-related dysfunctional anxiety. The Turkish validity and reliability of the scale were established by Biçer et al. (21). It consists of five-point Likert-type questions and one dimension and is scored as "0-never", "1-rarely, less than one or two days", "2-a few days", "3-more than seven days", and "4-almost every day in the last two weeks." The highest score obtainable from the scale is 20, and scores of nine and above indicate a high level of anxiety. The Cronbach's alpha value of the original version of the scale was 0.93 (20). The Cronbach's alpha value was 0.83 in the study of Biçer et al. (21), whereas it was found to be 0.80 in our study.

**Turkey Health Literacy Scale-32 (THLS-32):** The scale was developed by Okyay et al. (22) in 2016 based on the "European Health Literacy Survey (HLS-EU)" and its validity and reliability study was conducted. Unlike HLS-EU, THLS-32 has a 2x4 matrix structure instead of a 3x4 matrix structure and consists of 32 questions. Accordingly, it consists of eight components in total: the two dimensions are "protection from diseases/health promotion and treatment/service" and the four processes are "access to health information, understanding health information, appraisal of health information, and applying/using health information" (22). The Cronbach's alpha value was 0.92 in the study of Okyay et al. (22), whereas it was found to be 0.94 in our study.

According to the index score obtained, the level of health literacy is classified into the following four categories:

(0-24.99) points: insufficient health literacy,

(25-32.99) points: problematic-limited health literacy,

(33-41.99) points: sufficient health literacy,

(42-50) points: excellent health literacy.

### Ethical Consideration

Ethics committee approvals were obtained from the Amasya University Non-Interventional Clinical Research Ethics Committee (approval number: 15386878-044 July 03, 2020-13312 and E-15386878-044-32314 September 13, 2021-32314). In addition, written permission was obtained from the Turkish Ministry of Health Scientific Research Platform (-2020-06-10T18_35_08). Written informed consent was also obtained from the participants of the study. The Declaration of Helsinki was adhered to throughout.

### Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences 22 (IBM SPSS Corp., Armonk, NY, USA) program. Due to the non-normal distribution of the data, the Mann-Whitney U test was used in paired comparisons and the Kruskal-Wallis H test was used for comparisons between three or more groups. Spearman correlation analysis was used to determine the correlations between the scale scores. The relationship between categorical data was tested using chi-square analysis. The descriptive statistical method was used to evaluate the study data. The significance level was set at 0.05.

## Results

### Demographic and Disease-Specific Characteristics of Patients

The mean age of the patients was 60.68±13.04 (minimum-maximum: 20-83). Of these, 59% were female; 89% were married; 71% lived with their spouses and children; 43% had been diagnosed with cancer 3-6 months ago; and 51% had no comorbidities (Table 1). Of the patients, 72% were not diagnosed with COVID-19, whereas 91% followed the warnings about COVID-19 (Table 2).

### Distribution of THLS-32 and CAS-SF Scores and the Relationship between Them

The patients' total health literacy score was 26.73±12.44 (minimum-maximum: 0.00-47.89); the coronavirus anxiety score was 0.98±1.99 (minimum-maximum: 0.00-14.00); 33% of the patients had insufficient health literacy (12.19±8.98; minimum-maximum: 0.0-25); 39% had problematic-limited health literacy (29.90±2.89; minimum-maximum: 24-33); 21% had sufficient health literacy (37.36±2.28; minimum-maximum: 33-42); and 7% had excellent health literacy (45.81±2.06; minimum-maximum: 42-48). There was no significant correlation between health literacy and coronavirus anxiety total scores ($r=-0.079$; $p>0.05$). There was no significant difference between health literacy classifications and CAS scores ($H=0.657$; $p>0.05$).

### Comparison of Socio-Demographic and Disease-Specific Characteristics with Health Literacy and Coronavirus Anxiety Levels

There was no significant difference when the patients' sex, marital status, employment status, and financial status and their total scores on CAS-SF and THLS-32 were compared ($p>0.05$). While there was a significant difference between the education status, presence of comorbidities, and health literacy score ($p<0.05$), there was no significant difference between these characteristics and the total CAS-SF score ($p>0.05$). Patients with high levels of education and no comorbidities scored higher on health literacy and lower on coronavirus anxiety, whereas those with additional chronic diseases had higher anxiety scores (Table 3). The levels of health literacy of those whose income exceeded expenses, those who had been diagnosed with cancer 37 months ago or

**Table 1. Distribution of patients according to demographic and disease characteristics (n=100)**

| Variables | n | % |
|---|---|---|
| **Gender** | | |
| Female | 59 | 59.00 |
| Male | 41 | 41.00 |
| **Marital status** | | |
| Married | 89 | 89.00 |
| Single | 11 | 11.00 |
| **Education status** | | |
| Primary school | 73 | 73.00 |
| Middle school and above | 27 | 27.00 |
| **Employment status** | | |
| Employed | 19 | 19.0 |
| Unemployed | 81 | 81.0 |
| **Income status** | | |
| Income < expenses | 35 | 35.0 |
| Income = expenses | 58 | 58.0 |
| Income > expenses | 7 | 7.0 |
| **Social security** | | |
| Yes | 5 | 5.0 |
| No | 95 | 95.0 |
| **Cohabitants** | | |
| Alone | 7 | 7.0 |
| Nuclear family (spouse and/or children) | 71 | 71.0 |
| Extended family (spouse, children, family elders) | 13 | 13.0 |
| Other | 9 | 9.0 |
| **Cancer diagnosis** | | |
| Unspecified | 19 | 19.0 |
| Respiratory system (lung) | 9 | 9.0 |
| Gastrointestinal system (stomach, liver, colon) | 25 | 25.0 |
| Urinary system (prostate, bladder) | 9 | 9.0 |
| Endocrine system (pancreas, ovaries) | 15 | 15.0 |
| Breast | 23 | 23.0 |
| **Time of the first cancer diagnosis** | | |
| 3-6 months ago | 43 | 43.0 |
| 7-12 months ago | 24 | 24.0 |
| 13-24 months ago | 7 | 7.0 |
| 25-36 months ago | 13 | 13.0 |
| 37 months ago and earlier | 13 | 13.0 |
| **Chemotherapy status** | | |
| Yes | 92 | 92.0 |
| No | 8 | 8.0 |
| **Presence of comorbidities** | | |
| Yes | 49 | 49.0 |
| No | 51 | 51.0 |

| Table 2. COVID-19-related descriptive characteristics of patients (n=100) | | |
|---|---|---|
| **Variables** | **n** | **%** |
| **Diagnosis of COVID-19** | | |
| Yes | 28 | 28.0 |
| No | 72 | 72.0 |
| **Admission to hospital because of the suspicion of COVID-19** | | |
| Yes | 39 | 39.0 |
| No | 61 | 61.0 |
| **Diagnosis of a relative with COVID-19** | | |
| Yes | 50 | 50.0 |
| No | 50 | 50.0 |
| **Admission of a relative to the hospital because of suspicion of COVID-19** | | |
| Yes | 59 | 59.0 |
| No | 41 | 41.0 |
| **Status of watching news about COVID-19** | | |
| Yes | 92 | 92.0 |
| No | 8 | 8.0 |
| **Sources of information on COVID-19** | | |
| The website of the Ministry of Health and its instructions | 21 | 21.0 |
| TV, radio, and internet news | 75 | 75.0 |
| From the statements of the health personnel | 1 | 1.0 |
| Social media (Twitter, Instagram, Facebook, etc.) | 3 | 3.0 |
| **Training method preferred for instruction on COVID-19** | | |
| Social media training | 21 | 21.0 |
| Various videos distributed by phone | 16 | 16.0 |
| Distribution of brochures and posters | 8 | 8.0 |
| Oral presentation | 47 | 47.0 |
| Nothing interests me | 8 | 8.0 |
| **Paying attention to warnings regarding COVID-19** | | |
| Yes | 91 | 91.0 |
| No | 9 | 9.0 |
| **Delaying medical examinations due to COVID-19** | | |
| Yes | 23 | 23.0 |
| No | 77 | 77.0 |
| **Status of being affected by the treatment process when COVID-19 first appeared** | | |
| Not going to the hospital unless necessary when it first appeared | 80 | 80.0 |
| Not going to the health institution despite the need when it first appeared | 10 | 10.0 |
| Preferring telephone support from physicians and nurses | 9 | 9.0 |
| Benefiting from herbal mixtures that one knows or is recommended | 1 | 1.0 |
| **Changes in the patient's life due to the COVID-19 process*** | | |
| Leave treatment incomplete | 90 | 90.0 |
| Not wanting to go to the hospital | 41 | 41.0 |
| Fear of getting the virus | 67 | 67.0 |
| Fear of catching the virus every time I go to the hospital | 41 | 41.0 |
| Psychological state being negatively affected by being away from loved ones | 27 | 27.0 |
| Starting to be afraid of being in the same environment as other people | 51 | 51.0 |
| Fear of death | 22 | 22.0 |
| Starting to follow social media more | 11 | 11.0 |
| Starting to have obsessions with handwashing because of constant worry | 14 | 14.0 |
| Being tired/hating washing hands and wearing masks | 13 | 13.0 |
| Concern for the future | 6 | 6.0 |
| **The status of going to the health institution easily as the normalization process has started** | | |
| Yes | 63 | 63.0 |
| No | 3 | 3.0 |
| Does not go anyway unless necessary | 34 | 34.0 |

*Patients marked with multiple options, COVID-19: Coronavirus disease-2019

**Table 3. Comparison of health literacy and coronavirus anxiety levels with socio-demographic and disease-specific characteristics**

| | | Total Score of the Health Literacy Scale | | Total Score of the Coronavirus Anxiety Scale | |
|---|---|---|---|---|---|
| | | X ± SD | Min.-max. | X ± SD | Min.-max. |
| Gender | Female | 26.72±13.05 | 0.00-47.89 | 0.83±1.53 | 0.00-7.00 |
| | Male | 26.75±11.65 | 0.00-45.81 | 1.20±2.52 | 0.00-14.00 |
| Test statistics | | U=1183; p=0.853 | | U=1138.5; p=0.551 | |
| Marital status | Married | 26.67±12.10 | 0.00-47.89 | 1.07±2.09 | 0.00-14.00 |
| | Single | 27.26±15.56 | 2.08-47.89 | 0.27±0.65 | 0.00-2.00 |
| Test statistics | | U=429.5; p=0.508 | | U=392.5; p=0.201 | |
| Education status | Primary school | 25.48±11.95 | 0.00-47.89 | 1.08±2.23 | 0.00-14.00 |
| | Middle school and over | 30.12±13.31 | 2.08-47.89 | 0.70±1.14 | 0.00-4.00 |
| Test statistics | | U=710.5; **p=0.033** | | U=980.5; p=0.963 | |
| Employment status | Employed | 29.15±13.02 | 7.28-47.37 | 0.84±1.07 | 0.00-3.00 |
| | Unemployed | 26.17±12.31 | 0.00-47.89 | 1.01±2.16 | 0.00-14.00 |
| Test statistics | | U=648; p=0.286 | | U=682; p=0.357 | |
| Income status | Income < expenses | 26.09±13.12 | 0.00-47.89 | 0.46±0.92 | 0.00-4.00 |
| | Income = expenses | 26.71±12.43 | 0.00-47.89 | 1.33±12.45 | 0.00-14.00 |
| | Income > expenses | 35.17±3.25 | 30.71-40.60 | 0.71±0.95 | 0.00-2.00 |
| Test statistics | | U=5.124; p=0.077 | | U=2.444; p=0.295 | |
| Presence of comorbidities | Yes | 24.31±13.02 | 0.00-47.89 | 1.22±2.43 | 0.00-14.00 |
| | No | 29.07±11.49 | 0.00-47.89 | 0.75±1.44 | 0.00-7.00 |
| Test statistics | | U=950.5; **p=0.039** | | U=1111; p=0.253 | |
| Time of the first cancer diagnosis | 3-6 months ago | 25.78±13.35 | 0.00-47.89 | 0.88±1.73 | 0.00-7.00 |
| | 7-12 months ago | 27.89±10.05 | 4.68-47.89 | 1.46±2.92 | 0.00-14.00 |
| | 13-24 months ago | 26.18±14.03 | 0.00-40.60 | 0.86±1.21 | 0.00-3.00 |
| | 25-36 months ago | 26.43±13.59 | 1.56-47.37 | 0.92±1.55 | 0.00-5.00 |
| | 37 months ago and earlier | 28.35±12.89 | 0.00-42.69 | 0.54±1.45 | 0.00-5.00 |
| Test statistics | | U=0.927; p=0.921 | | U=3.365; p=0.499 | |
| Chemotherapy status | Yes | 26.95±12.32 | 0.00-47.89 | 0.97±2.02 | 0.00-14.00 |
| | No | 24.21±14.38 | 0.00-39.56 | 1.13±1.73 | 0.00-5.00 |
| Test statistics | | U=344.5; p=0.765 | | U=315.5; p=0.424 | |

SD: Standard deviation, Min.: Minimum, Max.: Maximum

earlier, and those who continued to receive chemotherapy were higher; however, there was no statistically significant difference between them. The coronavirus anxiety scores of patients who were married, were primary school graduates, were male, were unemployed, had comorbidities, were diagnosed with cancer 7-12 months ago, and did not receive chemotherapy were higher (Table 3).

There was no significant correlation between age and CAS-SF scores (r=0.104; p>0.05), whereas there was a negative and significant correlation between health literacy and age (r=-0.350; p<0.001). The level of health literacy of patients decreased as their age increased.

### Comparison of COVID-19-Related Variables with Levels of Health Literacy and Coronavirus Anxiety

The CAS-SF scores of patients who delayed their medical examinations because of COVID-19 were statistically significantly high (p<0.05) (Tablo 4). Even if there was no statistically significant difference, the coronavirus anxiety levels were high (p>0.05) amongst those who (or whose relatives) were diagnosed with COVID-19 and who (or whose relatives) attended the hospital because of the suspicion of COVID-19. The levels of health literacy of those who (and whose relatives) applied to the hospital due to COVID-19 and those whose relatives were diagnosed with COVID-19 were high, whereas the level of health literacy of those who were diagnosed with COVID-19 themselves was low (p>0.05) (Table 4).

## Discussion

Cancer diagnosis alone can cause feelings such as anxiety, worry, hypersensitivity, despair, and fear in patients. Although it was recommended to follow the isolation and hygiene rules that cancer patients are accustomed to, during the COVID-19 process, factors such as being away from loved ones, the absence of known drugs in the treatment of the disease, and the continuation of vaccine studies in the early stages of the pandemic all caused the patients to experience

**Table 4. Comparison of the levels of health literacy and coronavirus anxiety with variables related to COVID-19**

| | | Total Score of the Health Literacy Scale | | Total Score of the Coronavirus Anxiety Scale | |
|---|---|---|---|---|---|
| | | X ± SD | Min.-max. | X ± SD | Min.-max. |
| COVID-19 diagnosis | Yes | 26.68±13.04 | 0.00-47.37 | 1.32±2.96 | 0.00-14.00 |
| | No | 26.76±12.29 | 0.00-47.89 | 0.85±1.47 | 0.00-7.00 |
| Test statistics | | U=1002; p=0.963 | | U=990.0; p=0.872 | |
| Admission to the hospital because of suspicion of COVID-19 | Yes | 27.58±12.60 | 0.00-47.37 | 1.38±2.78 | 0.00-14.00 |
| | No | 26.20±12.40 | 0.00-12.40 | 0.72±1.23 | 0.00-5.00 |
| Test statistics | | U=1080; p=0.439 | | U=1129.5; p=0.612 | |
| Diagnosis of a relative with COVID-19 | Yes | 27.23±11.87 | 0.00-47.89 | 1.26±2.51 | 0.00-14.00 |
| | No | 26.23±13.08 | 0.00-47.89 | 0.70±1.27 | 0.00-5.00 |
| Test statistics | | U=1226.5; p=0.871 | | U=1147.0; p=0.397 | |
| Admission of a relative to the hospital because of suspicion of COVID-19 | Yes | 27.40±12.31 | 0.00-47.89 | 1.22±2.40 | 0.00-14.00 |
| | No | 25.77±12.71 | 0.00-47.89 | 0.63±1.13 | 0.00-4.00 |
| Test statistics | | U=1085.5; p=0.385 | | U=1100.5; p=0.360 | |
| Delaying medical examinations due to COVID-19 | Yes | 29.58±10.18 | 0.00-47.37 | 1.22±1.44 | 0.00-5.00 |
| | No | 25.88±12.97 | 0.00-47.89 | 0.91±2.13 | 0.00-14.00 |
| Test statistics | | U=741,5; p=0.238 | | **U=682; p=0.046** | |

COVID-19: Coronavirus disease-2019, SD: Standard deviation, Min.: Minimum, Max.: Maximum

anxiety, fear, and isolation (10,23). It is thought that the level of health literacy is important in coping with the effects of the pandemic, as the better the level of literacy, the better an individual will be at understanding the situation, making informed choices, and knowing what services to use.

In our study, it was determined that the levels of health literacy of the participants were low, that the majority had limited health literacy, and that the coronavirus anxiety scores were also low. Moreover, it was determined that the sources of information for 70% of the participants were television, radio, and internet news. Likewise, in a health literacy study conducted on the general population in Turkey, it was found that health literacy was low (17). Nguyen et al. (24) stated that one-third of cancer patients had limited health literacy, which resulted in more hospitalizations and emergency room visits. It was reported that health literacy in cancer patients (25) and in the general population (26) was low and that it was at a problematic level at a rate of 50.1% (27) during the COVID-19 pandemic.

The differences in national and international preventive and curative health policies followed during the pandemic process, the constant change in mortality and morbidity data, and the constant change of information about how the effects of the pandemic on hospital workload, the economy, education, and social life have affected the health literacy of health professionals and society as a whole, have made it difficult to track information (14). Good health literacy is of great importance to raise social awareness and take appropriate actions, especially in events that closely concern the health of all communities. Our findings showed that there was a need for actions and policies to improve health literacy in Turkey both before and during the pandemic (17). Furthermore, the development of reliable sources of information in multiple languages to combat the pandemic effectively will undoubtedly be valuable in the future success and control of the fight against the pandemic. In this regard, there is a need to determine the levels of health literacy of the whole of society, as understanding these levels will ensure that the information provided is as accessible and relevant to as broad a range of society as possible.

In our study, the coronavirus-related dysfunctional anxiety level of the patients was found to be low. This may be because the research process coincided with the process of life returning to normal. The initiation of vaccinations in Turkey at the time of the study and the consensus on measures for protection against the virus may have been effective. In addition, in our study, 90% of the participants left their treatment incomplete; 67% had a fear of getting the virus; 41% did not want to go to hospital; 51% began to be afraid of being in the same environment with other people; 14% started to have an obsession with washing hands; 13% got tired of washing hands and wearing masks and started to hate these restrictions. These can actually be considered as indicators of anxiety in individuals. In the literature, both during the pandemic and during the normalization process, the rate of anxiety due to coronavirus was reported to be 17.7% (28), 19.1% (29), 67.5% (30), and 47% (31); the rate of fear was 66% (29) and 62% (32). The differences in anxiety rates reported in the literature may be due to differences in measurement tools and the dates on which the studies were conducted. In their meta-analysis study, Ayubi et al. (33) emphasized that cancer patients experienced high levels of anxiety during the pandemic compared with normal healthy control groups and that depression was seen 60% more and anxiety was seen 30% more. Even after the first two waves of the pandemic, it was reported that the fear of getting COVID-19 was more dominant, especially in cancer patients who did not speak English and who used social media more frequently (32). The rapid spread of information to the larger masses due to technological developments

and the internet also causes the rapid spread of incorrect and correct information. The indemic has sabotaged vaccination efforts, causing fear and confusion (32). The knowledge and attitudes of individuals in the fight against an infectious disease can affect both individual and societal decision-making and change the course of the outbreak. Therefore, it is necessary to obtain information from reliable sources and thus improve social health literacy.

In our study, it was determined that education level and comorbidities were factors affecting health literacy. Patients with high levels of education and no comorbidities scored higher on health literacy and lower on coronavirus anxiety, whereas those with additional chronic diseases had higher anxiety scores. The higher the education level, the better the ability to access and synthesize information. In addition, the presence of comorbidities may have motivated individuals to reach for health-related information; thus, their health literacy levels were also high. Similarly, it has been reported in the literature that education level is an important factor affecting health literacy (13,15,26,30). Individuals with poor professional status, low income, and low education levels are less likely to access electronic sources of information and the internet. In this period, in which misinformation and rumors have spread and it has been difficult to distinguish between right and wrong, health professionals and policy implementers need to be more attentive and careful. Considering the limited resources and workforce, there is a need to determine the characteristics of society in the promotion and protection of health (15). A study conducted with adults in Australia showed that those with low health literacy had difficulty understanding COVID-19 symptoms, identifying protective behaviors against COVID-19, accessing information, and understanding messages (34). Health-related messages should be prepared to meet the needs of different groups; otherwise, they may pave the way for developing greater risks (34). In a study conducted in Saudi Arabia, it was stated that the public was afraid of COVID-19 more than average, which was associated with a low level of functional health literacy (26). Moussa et al. (26) stated that age, employment status, education level, and health literacy are predictors and important factors in the fear of COVID-19. Participants with higher levels of education performed better in using academic journals, filling out medical forms, and understanding and analyzing information (32).

While no significant correlation was determined between age and coronavirus anxiety scores in our study, there was a negative and significant correlation between health literacy and age and the level of health literacy decreased as age increased. In addition, the fact that the mean age of the study group was 60 and that 73% of the participants were primary school graduates can be associated with the difficulty in searching and accessing information, especially in following and synthesizing rapidly changing information during the pandemic. Technological confidence levels of individuals with advanced age and low health literacy are low (25). In a study conducted in Australia, it was determined that those aged 56-90 took the threat of COVID-19 more seriously than younger participants (34). Advanced age and low health literacy are both associated with a fear of COVID-19 (26).

In our study, the scores of patients who delayed their medical examinations on CAS-SF were high. This may be because patients were reluctant to go to the control examinations because of anxiety about getting the virus, and there was a high number of patients who said that they would not go to the hospital unless necessary. Similarly, in the literature, it was determined that cancer patients aged over 60 years in Turkey tended to postpone their tomography examinations more during the COVID-19 process and that they were worried about getting the virus (35).

In our study, it was observed that the level of health literacy was high in those who (and whose relatives) applied to the hospital because of COVID-19 and those whose relatives were diagnosed with COVID-19. This finding may be attributed to the fact that in cases of suspected COVID-19, and where their relatives got the virus, the participants obtained accurate information from health professionals, the process coincided with the normalization process, some information was clearer, and the same information was given everywhere, reducing the confusion.

In our study, the high level of health literacy in those who were diagnosed with cancer 37 months ago or earlier can be attributed to the fact that they met more frequently with health professionals, learned new information as time progressed, and developed compliance with the disease over time. Individuals with long-term chronic diseases can improve their health literacy skills and undergo medical examinations more regularly (36).

### Study Limitations

The fact that the study process coincided with the process of life returning to normal and that the findings could not be compared with those reported in the period when the number of active cases was higher can be considered as the limitations of the study.

## Conclusion

Because cancer patients with limited health literacy are at risk of disrupting their treatment plans during stressful processes such as pandemics, nurses should first determine patients' levels of health literacy. Age, education level, comorbidities, and the factor causing the pandemic should be considered while preparing training materials and content, and patients should be able to access accurate and reliable sources. Planning nursing initiatives that will increase health literacy is the key to a successful pandemic.

In conclusion, it was determined that cancer patients had limited health literacy and that those with advanced age, low education level, and comorbidities had even lower health literacy. Although no statistically significant difference was determined between them, the levels of health literacy of those who had an income that exceeded expenses, those who were diagnosed with cancer 37 months ago or earlier, and those who received chemotherapy treatment were higher. The results of this study can be used for a better understanding of the needs and concerns of cancer patients during the COVID-19 pandemic. They can also be used in healthcare planning and in foreseeing the concerns of patients receiving cancer treatment during potential future outbreaks of infectious diseases.

**Acknowledgements:** The authors would like to express their warm thanks to the patients who participated in this study.

**Ethics Committee Approval:** Ethics committee approvals were obtained from the Amasya University Non-Interventional Clinical Research Ethics Committee (approval number: 15386878-044 July 03, 2020-13312 and E-15386878-044-32314 September 13, 2021-32314).

**Informed Consent:** Written informed consent was also obtained from the participants of the study.

**Authorship Contributions:** Concept - E.T.; Design - E.T.; Data Collection or Processing - E.T., E.D.; Analysis or Interpretation - E.T., E.D.; Literature Search - E.T.; Writing - E.T., E.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 21-4
**DOI:** 10.4274/imj.galenos.2024.74044

# Angle Grinder Injuries in the Upper Extremity: An Epidemiological Study

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## ABSTRACT

**Introduction:** This study evaluated hand and forearm injuries caused by angle grinders and identify the risk factors.

**Methods:** Between 2020 and 2022, 79 patients with hand and forearm injuries due to angle grinder were retrospectively evaluated. Data were obtained from the hospital database and telephone interviews with patients. Age, gender, education level, employment status and work experience, smoking, and alcohol use were recorded. The injury location and structures were evaluated. The time of injury and use of protective gloves were recorded. The Modified Hand Injury Severity Score (MHISS) was used to determine the severity of the injury. The return to work times of actively working patients were recorded.

**Results:** Seventy-nine patients with angle grinder injuries were included in the study. All patients were male. Dominant side injury was in 17 (21.5%) patients. The most frequently injured area was the dorsal hand, and the most frequently injured structure was the extensor tendon. The mean MHISS was 49.15 (4-280) and 39 (49.4%) patients had minor injuries. The mean return to work was 7.13 (2-32) weeks. No correlation was found between age, work experience, and MHISS (p=0.167 p=0.389). There was a correlation between the use of protective gloves and MHISS (p=0.002).

**Conclusion:** Injuries to the hand and forearm caused by angle grinder usage can result in serious work-related disabilities. These injuries can be reduced by increasing safety precautions and training.

**Keywords:** Angle grinder, hand, injury

## Introduction

Acute traumatic hand and forearm injuries are traumas that lead to significant comorbidities and work disabilities. These injuries are common and have an incidence ranging from 57.4 (1) to 700 per 100,000 individuals (2). The return to work period is prolonged because of pain, post-traumatic stress disorder, and injury-related sequelae. In a study involving 91 patients, the average return to work period exceeded one year in 9% of cases, with a mean duration of 10.5 weeks (3).

One of the causes of acute traumatic hand injuries is the use of industrial tools such as angle grinders (4). Angle grinders are tools used to grind, polish, and cut various hard surfaces, including metal and concrete. Angle grinder injury is most common in the upper extremity after face and head injuries (5). According to data from "the Royal Society for the Prevention of Accidents" Accident Surveillance Systems, angle grinders are ranked as the third most dangerous tool, with 5,400 injuries recorded annually (6).

In this study, we evaluated patients who presented to our clinic following hand and forearm injuries caused by angle grinders and identified risk factors.

## Methods

The study was initiated with the approval of Baltalimanı Metin Sabancı Bone Diseases Training and Research Hospital Ethics Committee (approval number: 85, date: 02.08.2023). Verbal consent was obtained from all patients. A total of 589 patients with hand and forearm injuries between 2020 and 2022 were examined. Of these, 79 patients who were injured due to angle grinder were included in the study. The patient data were obtained from the hospital database and telephone conversations with the patients.

Age, gender, education level, employment status, work experience, smoking, and alcohol use were recorded.

It was recorded whether the injured and dominant sides were injured. Injury sites were determined as hand volar, hand dorsal, forearm volar, and forearm dorsal. The injured structures of the patients were recorded from the surgical notes (tendon, bone, vessel, nerve, amputation).

The injury time and use of protective gloves during injury were recorded.

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**Cite this article as:** Acar B, Şencan A, Baydar M, Ünkar EA, Ertem H, Uzun BA. Angle Grinder Injuries in the Upper Extremity: An Epidemiological Study. İstanbul Med J 2024; 25(1): 21-4.

**Received:** 12.12.2023
**Accepted:** 21.01.2024

The Modified Hand Injury Severity Score (MHISS) was used to determine the severity of the injury (7). Skin, skeletal, motor, and neurovascular structures were evaluated and graded. The score was doubled for open fractures, crush and avulsion injuries, and dirty wounds. The total score was recorded as <20 minor, 21-50 moderate, 51-100 severe, and >100 major injuries. Finally, the return to work time of actively working patients was recorded.

### Statistical Analysis

SPSS 25 program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. Correlation analysis was used to determine the relationship between quantitative data. Statistical significance was accepted as $p<0.05$.

## Results

Seventy-nine patients with hand and forearm injuries due to angle grinder were included in the study. The mean age was 46.08±12.87. All patients were male. The right extremity of Twenty (25.3%) patients and the left extremity of 59 (74.7%) patients were injured, and 17 (21.5%) patients had dominant side injuries.

Forty-three (54.4%) patients had primary school education, 32 (40.5%) patients had high school education, and 4 (5.1%) patients had university education. Sixty-eight (86.1%) patients were actively working and 11 (13.9%) patients were retired. Fifty-three (67.1%) of the injuries were work accidents.

None of the patients received specific safety training on angle grinder use. Seventeen patients stated that they received occupational safety training. Twelve (15.2%) patients were using protective gloves during injury (Table 1).

The injury times of the patients were evaluated at 2 h intervals. The most frequent time of injury was 14.00-16.00 (Figure 1).

Smoking was in 56 (70.9%) patients. The average smoking level was 13 packs/year. Fifteen (19%) patients used alcohol regularly. Alcohol use was in 2 patients at the time of injury.

Injury locations were determined as hand volar and dorsal and forearm volar and dorsal. There were hand dorsal injuries in 49 (62%) patients, volar forearm injuries in 15 (19%) patients, dorsal forearm injuries in 9 (11.3%) patients, and hand volar injuries in 6 (7.7%) patients.

More than one structure was injured in 57 of 79 patients. The most injured structure was the extensor tendon (49 patients) 11 patients had total amputation (Figure 2).

Injury severity was assessed using MHISS. The mean MHISS was 49.15 (4-280). 39 (49.4%) patients had minor injury, 17 (21.5%) patients had moderate injury, 12 (15.2%) patients had severe injury, 11 (13.9%) patients had major injury (Figure 3).

The mean time of return to work was 7.13 (2-32) weeks.

### Correlation Analysis

When the correlation analysis was evaluated, no correlation was found between age, work experience, and the severity of injury ($p=0.167$, $p=0.389$). There was a correlation between MHISS and the time to return to work ($r=0.804$, $p<001$). There was also a correlation between the use of protective gloves and the severity of injury ($p=0.002$). Since

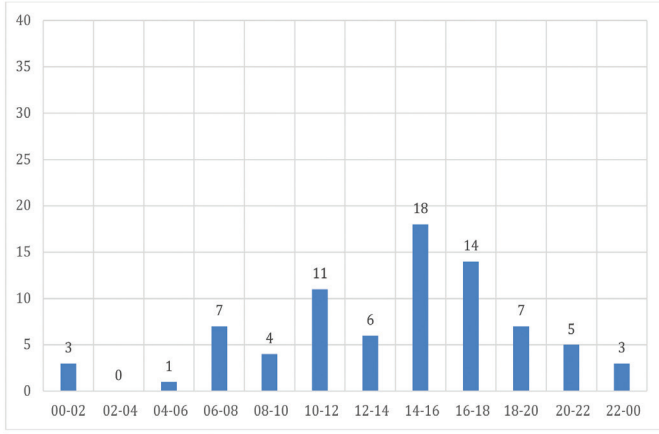


**Figure 1.** Distribution of the injury time

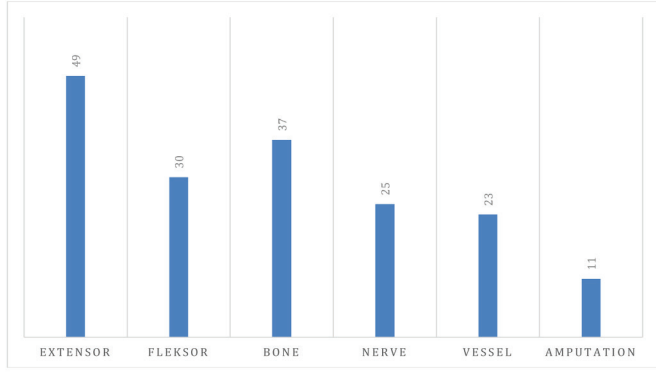


**Figure 2.** Distribution of injured structures

**Table 1. Demographic data**

| | | | |
|---|---|---|---|
| Age | 46.07±12.87 | | |
| Gender | Male (100%) | Female (0%) | |
| Side | Left (74.6%) | Right (25.4%) | |
| Dominant side | Yes (21.5%) | No (78.5%) | |
| Education | Primary (54.4%) | High (40.5%) | University (5.1%) |
| Protective glove | Yes (13.9%) | No (86.1%) | |
| Smoking | Yes (70.8%) | No (29.2%) | |
| Alcohol | Yes (18.9%) | No (81.1%) | |

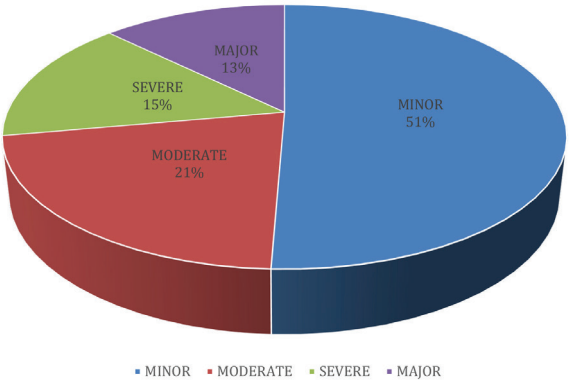


**Figure 3.** Distribution of Modified Hand Injury Severity Score (MHISS) groups

the number of patients who used alcohol at the time of injury was low, the correlation between alcohol use and injury could not be evaluated.

## Discussion

Angle grinders are high-speed industrial tools used for processing various surfaces such as metal and wood. When used incorrectly, it can lead to serious injuries (Figure 4).

In this study, we investigated hand and forearm injuries caused by the use of an angle grinder. However, when reviewing the literature, it was observed that facial injuries are the most common. This is attributed to the kick-back mechanism and the failure to use protective equipment (5,8).

Taboadela et al. (9), in their study with 928 patients, mentioned that only 8 patients were female. Approximately 4.96% of the patients had a university education. The most common time for injuries was between 12.00 and 20.00 (9). In the study conducted by Sozbilen et al. (10), 9% of the participants were university graduates, and the most common time for injuries was between 15.00 and 18.00. They also found no correlation between age, education level, smoking, alcohol consumption, and injury severity but identified a relationship with work experience (10). In the study conducted by Sorock et al. (11), which included 1,166 patients from 23 centers, approximately 76.4% of the patients were male, and the average age was 37.2±11.4. In our study, the demographic data were consistent with the literature. We did not observe a correlation between age, years of work experience, and injury severity.

According to the Global Adult Tobacco Survey Turkey 2016 report, 29.6% of the population engages in daily cigarette consumption (12). In our study, this rate is significantly higher within the community, at 70.9%. It is known that smokers tend to have weaker muscle strength and lower fatigue resistance. Nicotine possesses a suppressive property on the startle reflex (13). Additionally, nicotine withdrawal can lead to anxiety, depression, and difficulties in concentration (14). These factors suggest that smoking may increase the frequency of injuries. According to a report from the Turkish Ministry of Health in 2016, regular alcohol consumption in the general population was 12.2% (15). In our study, a similar figure was observed, with 19% reporting regular alcohol consumption. However, the impact of alcohol use during injuries was not examined, as only 2 patients reported alcohol consumption at the time of injury.


**Figure 4.** (a) Angle grinder (b-d) Samples of angle grinder injuries. Informed consent is taken from the patients

In our study, similar to the literature, extensor tendon injuries were observed most frequently. In one study, among 928 patients, extensor tendon injuries were present in 371 (39.9%) (9). Dębski and Noszczyk (6) reported tendon injuries in 56.1% of their patients.

The MHISS was used to assess the severity of injuries. In our study, the average score was 49.15 (range: 4-280), with 39 patients having minor injuries and 11 patients having major injuries. Taboadela et al. (9) reported 24.1% minor injuries and 26% major injuries. Kaya Bicer et al. (16) reported 11.63% major injuries in 43 patients.

Safety training and the use of protective equipment are crucial in reducing angle grinder injuries. In our study, we identified a correlation between the use of protective gloves and the severity of injuries. Sorock et al. (17) reported that out of 1165 patients, 225 (19.3%) used protective gloves, which were found to be protective against lacerations and puncture injuries. Garg et al. (18) also stated that the use of protective equipment reduces traumatic hand injuries.

Traumatic upper extremity injuries can lead to significant loss of work capacity (3). Izadi et al. (19) followed 280 patients for 3 months after injury and found that 45.7% of patients returned to work within 3 months, with an average return-to-work time of 57 days. Marom et al. (20) also reported a 75.3% return-to-work rate within 1 year and an average return-to-work time of 94 days. In our study, the average return-to-work time was 7.13 weeks (range: 2-32 weeks).

### Study Limitations

The limitations of our study are that it was retrospective and had no postoperative functional results. However, postoperative functional

results could not be evaluated because of the variety of injuries and differences in follow-up periods.

## Conclusion

Hand and forearm injuries associated with angle grinder use are serious injuries that can lead to significant morbidity and loss of productivity. Providing specific safety training for this industrial tool and increasing the use of protective equipment can help reduce such injuries.

**Ethics Committee Approval:** The study was initiated with the approval of Baltalimanı Metin Sabancı Bone Diseases Training and Research Hospital Ethics Committee (approval number: 85, date: 02.08.2023).

**Informed Consent:** Verbal consent was obtained from all patients.

**Authorship Contributions:** Surgical and Medical Practices - A.Ş., M.B., E.A.Ü.; Concept - B.A., M.B., H.E.; Design - B.A., A.Ş., B.A.U.; Data Collection or Processing - E.A.Ü., H.E., B.A.U.; Analysis or Interpretation - A.Ş., M.B., E.A.Ü.; Literature Search - B.A., H.E., B.A.U.; Writing - B.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 25-30
**DOI:** 10.4274/imj.galenos.2024.93827

# Quality of Information in YouTube Videos on Lateral Epicondylitis

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## ABSTRACT

**Introduction:** YouTube videos are commonly used by patients to learn more about their diseases. This study aimed to evaluate the quality of YouTube video content on lateral epicondylitis (LE).

**Methods:** We performed a search on YouTube using the keyword "lateral epicondylitis". The video source, video content, video duration, time since upload, number of views, comments, likes, and dislikes were recorded and evaluated. The popularity of the videos was determined using the Video Power Index (VPI). The quality and instructional value of the video were evaluated using the Global Quality Score (GQS), Lateral Epicondylitis Video Quality Score (LEVS), and DISCERN.

**Results:** Fifty-two of the 200 videos reviewed met the inclusion criteria. According to the video source, academic and physician videos had the highest quality, with no significant difference in DISCERN, GQS, or LEVS ($p>0.05$). VPI was significantly higher in physiotherapist videos than in academic and physician videos ($p<0.05$). The correlation between the video duration and quality score was significantly positive. The mean DISCERN, GQS, and LEVS scores for all included videos was respectively 41.7±19.6 (range: 15-75), 2.8±1.6 (range: 1-5), 5.7±2.8 (range: 2-10), respectively, indicating moderate quality. DISCERN scores, GQS, and LEVS given to videos by 2 independent physicians were strongly correlated (respectively $r=0.963$, $r=0.918$, $r=0.914$; and $p<0.001$ for all).

**Conclusion:** Although the videos of academics and physicians are of high quality, their viewing rates are low. YouTube videos on LE are of moderate quality.

**Keywords:** YouTube videos, lateral epicondylitis, DISCERN score, quality, internet

## Introduction

Lateral epicondylitis (LE), commonly referred to as tennis elbow, occurs due to injury affecting the tendons of the extensor digitorum communis and extensor carpi radialis brevis muscles at their attachment site on the bony prominence of the outer elbow (1). It is a common musculoskeletal disorder in the working population between the ages of 35 and 55 years (2). Patients typically complain of radiating pain from the lateral aspect of the elbow to the forearm, which affects most daily activities (3).

Anti-inflammatory medications, physical therapy (including activity modification, hot-cold application, rest and movement restriction, electrotherapy, massage, and ultrasound), extracorporeal shock wave therapy, splinting, laser, local injections (platelet-rich plasma and corticosteroids), and surgery have all been used to treat LE (4). In a disease with so many treatment methods, patients turn to the internet to determine what the treatments are, how they are applied, what they can do at home, or what they should pay attention to.

Digital resources and social networking platforms are assuming a growing significance in matters concerning health, becoming pivotal sources of information for numerous patients (5,6). The 2018 Health Information National Trends Survey in the United States found that over a third of patients watched health-related videos on YouTube (7). YouTube is an increasingly used video-sharing database for the acquisition of health information (5,8). It is the second most visited website worldwide, the second most popular social media network globally, a global social network translated into 80 different languages, used in 100 countries, and has more than 2 billion users (9-11). It is simple and free to upload videos to YouTube. At the same time, because there is no quality control method or peer assessment to determine the accuracy of these videos, patients may be exposed to false or misleading information. Studies on the quality and reliability of various diseases such as fibromyalgia, rheumatoid arthritis, and disk herniation have been conducted (12-14). The purpose of this study was to determine whether YouTube is a reliable and valid source of patient information about LE.

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**Cite this article as:** Ustabaşıoğlu F. Quality of Information in YouTube Videos on Lateral Epicondylitis. İstanbul Med J 2024; 25(1): 25-30.

**Received:** 21.11.2023
**Accepted:** 22.01.2024

## Methods

This study used a register-based, cross-sectional methodology to examine YouTube searches for "lateral epicondylitis" on January 15, 2022. All video searches were performed without logging in or changing the website's default search settings by deleting all search history. We examined the first 200 videos that came up when we searched for the given term. Videos with duplicate segments, videos under 60 seconds, videos not in English, and videos unrelated to LE were excluded.

Video source (academics, physician, physiotherapist, private clinic, health channel, personal trainer, chiropractor), video content (general information, injection, transcutaneous electrical nerve stimulation (TENS) therapy, surgical treatment technique, exercise therapy, ultrasonographic treatment, massage therapy, kinesio taping, diagnostic tests), video duration (seconds), and viewer engagement metrics such as total views, likes, dislikes, comments, and days the video was broadcast were documented for each video.

The daily count for each parameter (such as views and likes) was calculated by dividing the parameter by the total number of days the video was available for viewing. The Video Power İndex (VPI) defined by Erdem and Karaca (15) was used to assess the popularity of videos using the following formula: (number of likes/number of likes + number of dislikes) 100.

The DISCERN scoring system evaluates the dependability of a publication and the quality of treatment options information provided to the patient. There are 15 questions, each of which can score 1-5 points (5= declaring that the quality standards have been reached, 2-4= declaring that the quality standards have been partly reached, 1= declaring that the quality standards have not been reached). This scoring system assesses the objectivity and exhaustibility of medical information, particularly regarding treatment. The first section contains eight questions that assess a publication's dependability. The second section contains seven questions that assess treatment-related data (16). The DISCERN scoring system ranges from 15 to 75 points. If the study receives 63-75 points, it is considered high quality. Good quality is worth 51-62 points, fair quality is worth 39-50 points, poor quality is worth 27-38 points, and very poor quality is worth 15-26 points (17,18).

The Global Quality Score (GQS), developed by Bernard et al. (19), is a rating system used to evaluate the educational value of films meant for patient viewing. Users can use the GQS system to assess the quality of the video content. GQS considers information quality, accessibility, general information flow, and how beneficial it would be to any user (20). One point is assigned to poor quality, and five points to excellent quality.

We devised the Lateral Epicondylitis Video Quality Score (LEVS) as an evaluation metric for video quality. Scores were given as 0 to 3 points for information content of what causes LE, 0 to 4 points for information about treatment, and 0 to 3 points for knowledge of symptoms. The scores obtained in LEVS were summed to obtain a score between 0 and 10 for each video. Videos were categorized on the basis of their total scores: 0-2 points indicated very poor quality, 2-4 points denoted poor quality, 4-6 points suggested medium quality, 6-8 points signified good quality, and 8-10 points represented excellent quality.

DISCERN, GQS, and LEVS were used to assess the video content quality. Detailed information about DISCERN, GQS, and LEVS is presented in Table 1.

Two physiatrists who were blinded to each's results assessed all the videos. First, the intraclass correlation coefficient (ICC) was calculated to measure the consistency of the scores of the two physiatrists, and an agreement power greater than 0.95 was obtained for all scoring systems. For statistical purposes, the average of the two physiatrists' scores was used.

This study obtained ethical approval from the Trakya University Faculty of Medicine Ethics Committee (approval number: 08/20, date: 29.03.2021).

### Statistical Analysis

Statistical analyses were performed using SPSS commercial software (SPSS version 20.0, SPSS, Chicago IL, USA). Means and standard deviations for normally distributed variables are presented as numerical descriptive statistics. The percentages represent descriptive statistics for categorical variables. The Kolmogorov-Smirnov test was used to assess data normality.

A t-test for independent samples was used to compare the two independent groups. The ANOVA test was performed on three independent groups using Bonferroni correction. The association between the numerical variables was determined using Pearson's correlation test. The reliability of the two physiatrists' scores was assessed using the ICC. The significance level was considered $p<0.05$.

## Results

Of the 200 videos, 148 were eliminated from the study for the reasons listed below: of the videos, 39 had a duration of less than 60 s, 16 were presented in a language other than English, 51 contained information about diseases other than LE, and 42 were duplicates. Most videos were posted by physiotherapists (34,6%; n=18), followed by physicians (25%; n=13), academicians (9,6%; n=5), chiropractors (9,6%; n=5), private clinics (7,7%; n=4), personal trainers (7,7%; n=4), and health channels (5,8%; n=3).

When we look at the video content, the most content topic is general information about the disease (30,8%; n=16), followed by exercise (28,9%; n=15). Other treatments include surgical treatment technique (11,5%; n=6), diagnostic tests (7,7%; n=4), kinesio taping (7,7%; n=4), massage therapy (5,8%; n=3), injection (3,8%; n=2), TENS therapy (1,9%; n=1), and ultrasonographic treatment (1,9%; n=1). The video contents according to the source are shown in Table 2.

There was a strong correlation between the DISCERN scores, GQS, and LEVS that two separate physiatrists assigned to the videos (respectively $r=0.963$, $r=0.918$, $r=0.914$; and $p<0.001$ for all).

This study found no significant correlation between viewer interactions, VPI, and the values of the three scoring systems. The correlation between video duration and quality scorewas significantly positive. Table 3 shows the relationship between the video duration, user interactions, and VPI with quality. VPI was significantly higher in physiotherapist videos than in academic and physician videos ($p<0.05$).

**Table 1. DISCERN, Video Quality, and Global Quality Scoring Systems**

| DISCERN Scoring System | | | Lateral Epicondylitis Video Quality Score System | |
|---|---|---|---|---|
| **Question no** | **What is being investigated?** | **Question rate** | 0-3 | Availability of information about the pathogenesis/disease mechanism of LEVS. |
| **Section 1. Is the publication reliable?** | | | | |
| 1 | Are the aims clear? | 1-5 | 0-3 | Availability of information about symptoms and complications that may occur during LEVS. |
| 2 | Does it achieve its aims? | 1-5 | | |
| 3 | Is it relevant? | 1-5 | | |
| 4 | Is it clear what sources of information were used to compile the publication (other than the author or producer) | 1-5 | 0-4 | Availability of information about all treatment methods and duration of treatment for LEVS. |
| 5 | Is it clear when the information used or reported in the publication was produced? | 1-5 | | |
| 6 | Is it balanced and unbiased? | 1-5 | | |
| 7 | Does it provide details of additional sources of support and information? | 1-5 | | |
| 8 | Does it refer to areas of uncertainty? | 1-5 | | |
| **Section 2. How good is the quality of information regarding treatment choices?** | | | **Global quality scoring system** | |
| 9 | Does it describe how each treatment works? | 1-5 | 1 | Poor quality, very unlikely to be of any use to patients. |
| 10 | Does it describe the benefits of each treatment? | 1-5 | 2 | Poor quality but some information present, of very limited use to patients. |
| 11 | Does it describe the risks of each treatment? | 1-5 | | |
| 12 | Does it describe what would happen if no treatment was used? | 1-5 | 3 | Suboptimal flow, some information covered but important topics missing, somewhat useful to patients. |
| 13 | Does it describe how treatment choices affect the overall quality of life? | 1-5 | | |
| 14 | Is it clear that there may be more than 1 possible treatment choice? | 1-5 | 4 | Good quality and flow, most important topics covered, and useful to patients. |
| 15 | Does it provide support for shared decision making? | 1-5 | 5 | Excellent quality and flow, highly useful for patients. |

LEVS: Lateral Epicondylitis Video Quality Score

**Table 2. Video contents according to the source**

| Video content | Academic society, n (%) | Physician, n (%) | Physio-therapist, n (%) | Personal trainer, n (%) | Private clinic, n (%) | Health channel, n (%) | Chiropract, n (%) |
|---|---|---|---|---|---|---|---|
| General information | 2 (40) | 8 (61.5) | - | - | - | 3 (100) | 1 (20) |
| Exercise therapy | - | 1 (7.7) | 8 (44.4) | 4 (100) | 2 (50) | - | - |
| Injection | 1 (20) | 1 (7.7) | - | - | - | - | - |
| Surgical technique | 2 (40) | 2 (15.4) | - | - | 2 (50) | - | - |
| Massage therapy | - | - | 3 (16.7) | - | - | - | - |
| Kinesio taping | - | - | 2 (11.1) | - | - | - | 4 (80) |
| TENS therapy | - | - | 1 (5.6) | - | - | - | - |
| Diagnostics tests | - | - | 4 (22.2) | - | - | - | - |
| Ultrasonographic treatment | - | 1 (7.7) | - | - | - | - | - |
| Total | 5 | 13 | 18 | 4 | 4 | 3 | 5 |

The mean DISCERN score for the included videos was 41.7 19.6 (range: 15-75), indicating a moderate level of quality. Similarly, the average GQS for all videos was 2.8 1.6 (range: 1-5), indicating moderate quality. Furthermore, the mean LEVS for the videos was 5.7 2.8 (range: 2-10), indicating a moderate level of quality. Table 4 details the distribution of video distributions across scoring systems based on quality.

According to the video source, academic society and physician videos had the highest quality, with no significant difference in DISCERN, GQS, and LEVS ($p>0.05$). The quality of videos uploaded by physiotherapists, private clinics, health channels, personal trainers, and chiropractors were significantly lower, with no statistical difference. While Table 5 shows the average values of video quality according to the video source, Table 6 shows a statistical comparison of these values.

## Discussion

YouTube is a universally accessible and popular channel for health information that is free, multilingual, and easy to search. In addition, it is a visual environment with a low literacy requirement (21).

**Table 3. Mean values and correlation between user interactions and video duration by quality scores**

| | Mean ± SD | Min.-max. | DISCERN | | GQS | | LEVS | |
|---|---|---|---|---|---|---|---|---|
| | | | R-value | p-value | R-value | p-value | R-value | p-value |
| Days the video was broadcast | 1537.5±1030.7 | 107-4354 | | | | | | |
| Video duration | 306.8±283.4 | 74-1834 | 0.529 | <0.001 | 0.510 | <0.001 | 0.538 | <0.001 |
| Total views | 150312.9±373098.3 | 368-2186184 | -0.023 | 0.870 | -0.020 | 0.887 | -0.154 | 0.277 |
| Total likes | 1089.3±3413.7 | 6-24000 | 0.114 | 0.420 | 0.083 | 0.560 | 0.034 | 0.812 |
| Total dislikes | 37.5±97.9 | 0-548 | 0.103 | 0.469 | 0.093 | 0.512 | -0.021 | 0.882 |
| Total comments | 52.2±162.0 | 0-1137 | 0.164 | 0.245 | 0.136 | 0.336 | 0.088 | 0.535 |
| View ratio | 97.7±231.3 | 0.5-1268 | 0.031 | 0.828 | 0.044 | 0.757 | 0.012 | 0.931 |
| Like ratio | 95.2±4.7 | 78.2-100 | -0.186 | 0.188 | -0.196 | 0.163 | -0.189 | 0.179 |
| VPI | 1324.6±7686.8 | 0.4-54831 | 0.027 | 0.848 | 0.041 | 0.775 | -0.120 | 0.396 |

SD: Standard deviation, GQS: Global Quality Score, LEVS: Lateral Epicondylitis Video Quality Score, VPI: Video Power Index

**Table 4. Distribution of all videos in the scoring systems according to quality**

| Quality | DISCERN | | GQS | | LEVS | | Average percentage (%) |
|---|---|---|---|---|---|---|---|
| | Number of videos | Percentage (%) | Number of videos | Percentage (%) | Number of videos | Percentage (%) | |
| Very poor | 12 | 23.1 | 12 | 23.1 | 10 | 19.2 | 21.8 |
| Poor | 11 | 21.2 | 9 | 17.3 | 12 | 23.1 | 20.5 |
| Moderate | 12 | 23.1 | 14 | 26.9 | 10 | 19.2 | 23.1 |
| Good | 8 | 15.4 | 10 | 19.2 | 9 | 17.3 | 17.3 |
| Excellent | 9 | 17.3 | 7 | 13.5 | 11 | 21.2 | 17.3 |

GQS: Global Quality Score, LEVS: Lateral Epicondylitis Video Quality Score

**Table 5. Distribution of mean values by video unloaders in all scoring systems**

| Video uploader | DISCERN | | GQS | | LEVS | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Range | Mean ± SD | Range | Mean ± SD | Range |
| Academic society | 64.6±12.3 | 46.0-73.0 | 4.4±0.9 | 7.0-9.0 | 8.8±1.6 | 6.0-10.0 |
| Physician | 59.5±9.7 | 44.0-75.0 | 4.1±0.6 | 2.5-9.5 | 8.2±1.3 | 6.0-10.0 |
| Physiotherapist | 33.9±17.5 | 15.0-73.0 | 2.3±1.2 | 1.5-9.0 | 4.6±2.6 | 2.0-10.0 |
| Private clinic | 33.3±13.9 | 15.0-48.0 | 2.3±1.0 | 1.0-8.0 | 4.3±1.7 | 2.0-6.0 |
| Chiropractor | 32.8±15.5 | 16.0-47.0 | 2.2±1.1 | 1.0-7.0 | 4.4±2.2 | 2.0-6.0 |
| Health channel | 25.0±9.2 | 15.0-48.0 | 1.7±0.6 | 1.0-9.0 | 3.3±1.2 | 2.0-4.0 |
| Personal trainer | 22.5±9.0 | 15.0-33.0 | 1.5±0.6 | 1.0-3.0 | 3.0±1.2 | 2.0-4.0 |

GQS: Global Quality Score, LEVS: Lateral Epicondylitis Video Quality Score, SD: Standard deviation

Recent research has shown that Internet use is increasing among people to better understand their health problems and the treatment they receive (22,23). Therefore, although YouTube is a powerful tool for obtaining medical information, people should be careful when obtaining medical information from YouTube. Anyone from anywhere in the world can upload a video to YouTube without supervision and standardization. We know that low-quality health information obtained from YouTube negatively affects the doctor's relationship with the patient (23). Keelan et al. (24) conducted the first YouTube video study to assess the quality and reliability of medical information. Recently, articles that discuss the content, quality, and reliability of health-related videos posted on YouTube have become very popular (25,26). In this study, our primary objective was to assess the quality of YouTube videos related to LE.

In our study, 52 videos examined were viewed 150312 times on average. In a study examining 238 videos containing osteoporosis, it was reported that the mean number of views was 4719 (27). In a study evaluating 58 videos with musculoskeletal ultrasound content on YouTube, it was reported that the mean number of views was 6503 (28). The fact that the topics are different may be the reason for the difference in the number of views.

Most videos in our study were uploaded by physiotherapists. While the academics and physicians provide information about the disease and interventional procedures, the physiotherapists provide information about the exercises. The high VPI of physiotherapists reveals that patients do not want to learn what the disease is, but what exercises they can do to heal themselves at home. In addition, the fact that the

**Table 6. Statistical comparison of the mean values of video unloaders in 3 scoring systems**

| Video source | vs | Video source | DISCERN, (p) | GQS, (p) | LEVS, (p) |
|---|---|---|---|---|---|
| Academic society | vs | Physician | >0.05 | >0.05 | >0.05 |
| Academic society | vs | Physiotherapist | **0.002** | **0.001** | **0.002** |
| | vs | Private clinic | **0.037** | **0.034** | **0.029** |
| | vs | Chiropractor | **0.018** | **0.014** | **0.022** |
| | vs | Health channel | **0.008** | **0.006** | **0.010** |
| | vs | Personal trainer | **0.001** | **0.001** | **0.002** |
| Physician | vs | Physiotherapist | **<0.001** | **<0.001** | **<0.001** |
| | vs | Private clinic | **0.045** | **0.035** | **0.027** |
| | vs | Chiropractor | **0.016** | **0.011** | **0.017** |
| | vs | Health channel | **0.008** | **0.035** | **0.009** |
| | vs | Personal trainer | **0.001** | **<0.001** | **0.001** |
| Physiotherapist | vs | Private clinic | >0.05 | >0.05 | >0.05 |
| | vs | Chiropractor | >0.05 | >0.05 | >0.05 |
| | vs | Health channel | >0.05 | >0.05 | >0.05 |
| | vs | Personal trainer | >0.05 | >0.05 | >0.05 |
| Private clinic | vs | Chiropractor | >0.05 | >0.05 | >0.05 |
| | vs | Health channel | >0.05 | >0.05 | >0.05 |
| | vs | Personal trainer | >0.05 | >0.05 | >0.05 |
| Chiropractor | vs | Health channel | >0.05 | >0.05 | >0.05 |
| | vs | Personal trainer | >0.05 | >0.05 | >0.05 |
| Health channel | vs | Personal trainer | >0.05 | >0.05 | >0.05 |

Statistically significant values are presented in bold. GQS: Global Quality Score, LEVS: Lateral Epicondylitis Video Quality Score

viewers are far from medical terminology may explain their preference for physiotherapists who prefer a simpler language than academics and physicians. The academic physician videos become boring and unintelligible after a while, as it becomes difficult to bring their complicated medical information to a baseline level. On the other hand, physiotherapists provide more limited medical information and show exercise examples rather than details of the disease in their videos.

When the unloaders were examined, the videos uploaded by academics and physicians had the highest quality with no significant difference in DISCERN, GQS, and LEVS. On the other hand, videos uploaded by physiotherapists had significantly lower quality. This outcome indicates that academics and physicians are reliable but not popular compared with physiotherapists. Academics and physicians should try to upload educational videos with high popularity to have a better impact on society, and the long-term effects of this should be investigated with more comprehensive studies. Information on the internet is really valuable because it is difficult for people to reach hospitals, they cannot spare time for examination, and some diseases can only be cured with exercise. Unfortunately, since the information uploaded to the internet has not been audited, it is not right to trust it completely. Therefore, when searching for health-related information on the internet, attention should be paid to the source of the information.

This is the third study on LE YouTube videos in the English literature. The first research was published by Karagoz et al. (29), and the second was published by Özcan and Gürçay (30). The first study found no significant correlation between video source and DISCERN and GQS scores, whereas we and Özcan and Gürçay (30) found that the videos uploaded by physicians and academics have the highest quality. Although they found that YouTube videos on LE donot provide moderately sufficient information, we found that they provide moderate quality. The results were incompatible among the three studies, despite the identical topic. Because the content on YouTube changes so quickly, the videos on the first pages are constantly changing. These two studies were conducted at different times; therefore, the videos watched are probably different. This shows that if research on YouTube videos is performed at different times, the results will be different because the videos watched also change.

### Study Limitations

This study has some limitations that should be considered. The first limitation of this study is that YouTube has a very dynamic structure. Content is constantly changing. According to the search date and time, the results can change. The fact that the GQS is an extremely subjective scoring is the second limitation of our study, and we aimed to eliminate this subjectivity by performing each assessment twice by two separate authors. The third limitation, in order of popularitywas included the top 52 videos on YouTube for “lateral epicondylitis.” This search approach missed several videos that had a small number of views but could be of great 5-quality.

## Conclusion

Our study showed that YouTube videos on LE have moderate quality. Video quality is significantly associated with the upload source. Health-

related videos should be verified before they are uploaded to ensure that viewers have access to the correct information they need about health. Therefore, health-related content must be uploaded by experts. To achieve this, new studies should be conducted to prepare appropriate software.

**Ethics Committee Approval:** This study obtained ethical approval from the Trakya University Faculty of Medicine Ethics Committee (approval number: 08/20, date: 29.03.2021).

**Informed Consent:** Informed consent was obtained from all individual participants included in the study.

**Financial Disclosure:** The author declared that this study received no financial support.

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İstanbul Med J 2024; 25(1): 31-5
**DOI:** 10.4274/imj.galenos.2024.74484

# Are Recommendations Followed after Total Hip Arthroplasty? A Questionnaire

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## ABSTRACT

**Introduction:** Total hip arthroplasty (THA) is an operation that is successfully performed in patients with end-stage hip osteoarthritis. In this study, we aimed to evaluate the compliance level of primary THA patients with their doctor's post-operative advice on restricted hip movements and environment modifications to prevent dislocation.

**Methods:** A survey consisting of 14 questions was prepared, questioning 320 patients who underwent THA in our clinic between 2015 and 2021. One hundred and forty three patients agreed to participate in our study, and their answers regarding whether they followed the introductions recommended by the surgeon who performed the surgery were recorded.

**Results:** 99% of the 143 patients who participated in the survey stated that they were given some advice. 46% (n=66) of the patients stated that they were told that these introductions should be applied for life. 60% of the patients did not cross their legs, 74% did not squat, 86% did not sit cross-legged, 76% did not use toilet risers, and 89% do not do unrecommended sports.

**Conclusion:** Most patients complied with the surgeon's recommendations in the early period; however, we observed that compliance decreased over time.

**Keywords:** Arthroplasty, dislocation, exercise, hip, motion, prosthesis, postoperative recommendations, recommendations, restriction

## Introduction

Total hip arthroplasty (THA) is a successful option for patients with end-stage hip osteoarthritis (1). Dislocation after arthroplasty is an important complication seen in 2-9% of patients (2). To prevent hip dislocation after THA, surgeons give some traditional recommendations. These recommendations include sitting high (with a cushion); avoiding sports such as running, jumping, cycling, and using a European toilet; and avoiding squatting and crossing legs while sitting (3,4).

In recent years, developments in hip prosthesis designs and surgical techniques, the use of larger heads, better definition and evaluation of hip-lumbar pathologies and their evaluation (5), and the introduction of modern implants aiming to reduce the risk of dislocation have reduced the risk of dislocation after THA (6). A clear consensus has not yet been made on whether conventional recommendations after THA are still necessary. The issue of whether patients comply with these recommendations has not been properly investigated (7). In addition, there is no clear data on the percentage of patients following these recommendations, whether the degree of compliance reduces the complication rates, or to what extent it affects the functions and quality of life of these patients.

In this study, we evaluated the compliance level of primary THA patients with their doctor's post-operative advice on restricted hip movements and environment modifications.

## Methods

A survey consisting of 14 questions was prepared (Table 1), questioning 320 patients who underwent THA in our clinic between 2015 and 2021 by phone. Of the 143 patients who agreed to participate in our study, their answers regarding whether they followed the introductions recommended by the surgeon who performed the surgery were recorded. All questions were multiple-choice.

Patients who underwent primary THA for primary degenerative coxarthrosis, femoral neck fractures, and avascular necrosis of the femoral head with a follow-up period of at least one year were included in the study.

Patients who underwent revision surgery for THA, those diagnosed with a connective tissue disorder, and those with developmental hip dysplasia were excluded. The patients were informed about the questionnaire,

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**Cite this article as:** Demir B, Azboy N, Rakkad N, Ayasgil M, Çatal B, Azboy İ. Are Recommendations Followed after Total Hip Arthroplasty? A Questionnaire. İstanbul Med J 2024; 25(1): 31-5.

**Received:** 21.12.2023
**Accepted:** 23.01.2024

and their informed consent was obtained. Questions were asked to the patients by telephone interview. The responses were recorded.

The study protocol was approved by the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval number: 18, date: 05.01.2023). This study was conducted in accordance with the principles of the Declaration of Helsinki.

### Statistical Analysis

To measure whether the data were normally distributed or not was analyzed using the Kolmogorov-Smirnov test. Normally distributed continuous variables are given as mean ± standard deviation, and non-normally distributed as median (minimum-maximum). The chi-square test was used to compare the categorical data of the binary groups. A $p<0.05$ was considered statistically significant. The IBM SPSS version 25.0 (Chicago/Illinois, USA) data package program was used.

## Results

99% of the 143 patients who participated in the survey stated that they were indeed given some recommendations after THA. 46% (n=66) of the patients stated that they were told that this recommendation should be applied lifelong, whereas 13% (n=19) stated that the recommendations were for three months. While 36% of the patients stated that they would apply the recommendations lifelong, we determined that 6% of the patients (n=9) never followed the recommendations. 73% of the patients in our study were women, and their mean age was 68.1±16.2 years (Table 2). The mean follow-up time of this study was 3,9 years, ranging from 1 to 7 years.

Two patients (nearly 1%) had a dislocation. One was due to acetabular aseptic loosening and polyethylene wear at the end of the second year postoperatively, and the other was a periprosthetic fracture dislocation due to falling accidentally one month after the operation. Both were operated on after a femoral neck fracture. They agreed that doctors gave them advice, and they stated advice was for 6 months and lifelong, respectively. In addition, the former took the advice accordingly and the latter one for 1 year only.

When asked about the activities, the most frequently avoided activity by the patients was cycling (91%), followed by unrecommended sports (89%) Crossing their legs (60%) and squatting (74%). It was observed that 9% of the patients continued to perform squats and 6% performed cross-legged movements contrary to recommendations. 76% of the patients did not use WC risers, whereas 14% continued to use oriental toilets.

It was found that 63% of women in our study never crossed their legs, whereas this rate was 54% in men (p=0.017) (Table 3). In addition, the percentage of women avoiding squatting (80%) was significantly higher than that of men (59%) (p=0.022). Furthermore, the frequency of women never driving was 11%, in contrast, this rate was 18% in men (p=0.001). Likewise, women were slightly more compatible compared to men about not running, 84% to 72%, respectively (p=0.007).

## Discussion

This study demonstrated that almost all orthopedic surgeons (99%) give some recommendations to their patients to reduce the risk of dislocations after THA. Similarly, patients acknowledge that they have been given advice regarding physical activity restrictions. While most physicians made these recommendations for life-long implementation, only 39 (n=56) of patients adhered to them for relatively short periods, between 3 months and 1 year. It can be argued that patients tend to stop applying these recommendations.

The effect of recommendations to prevent dislocation is not adequately investigated. A review conducted in 2015 to investigate the effect of different patient restriction protocols on dislocation in primary THA stated that the follow-up period was between 6 months and 2 years. They analyzed studies including patients with a variable range of restriction protocols, stating that crossing legs and extreme hip flexion were the most common restrictions. They found a 1.5% dislocation rate in the restricted group and 1% in the unrestricted group. Their conclusion was that more liberal protocols would not increase dislocation rates (8). Accordingly, Peak et al. (9) studied the role of additional patient restrictions besides the range of hip motion (restriction of above 90 degrees flexion, adduction (crossing the legs), and internal and external rotation above 45 degrees, for all patients) on early dislocation following

**Table 1. These questions designed to measure patients' compliance with the recommendations of their surgeon**

| |
|---|
| Question 1. What was the reason for the surgery? |
| Question 2. What was the academic title of the physician who performed your surgery? |
| Question 3. Did your surgeon recommend you not to do some movements and activities? |
| Question 4. For what period did your surgeon recommend you not to perform some movements and activities to prevent prosthesis dislocation? |
| Question 5. How long did you apply the restrictions that your doctor recommended to you to prevent prosthesis dislocation? |
| Question 6. How often do you sit with your legs crossed? |
| Question 7. How often do you squat or bend over to pick up something on the floor? |
| Question 8. How often do you sit on the floor and walk cross-legged? |
| Question 9. Do you use a toilet lifter? |
| Question 10. Do you use a European toilet? |
| Question 11. When did you start driving a vehicle after surgery? |
| Question 12. How often do you cycle? |
| Question 13. How often do you run? |
| Question 14. How often do you participate in sports like football, basketball, or tennis? |

**Table 2. Demographic characteristics of the patients and questionnaire responses (n=143)**

| | | n | % |
|---|---|---|---|
| Gender | Female | 104 | 72.7 |
| | Male | 39 | 27.3 |
| Reason for the operation | Osteoarthritis | 111 | 77.6 |
| | Avascular necrosis | 3 | 2.1 |
| | Fracture | 29 | 20.3 |
| Surgeon's title | Orthopedic Surgeon Dr. | 16 | 11.2 |
| | Associate. Prof. Dr. | 77 | 53.8 |
| | Prof. Dr. | 50 | 35.0 |
| Compliance with the recommendations | Yes | 142 | 99.3 |
| | No | 1 | 0.7 |
| Recommendation period | 3 months | 19 | 13.3 |
| | 6 months | 23 | 16.1 |
| | 1 year | 15 | 10.5 |
| | 3 years | 20 | 14.0 |
| | Lifelong | 66 | 46.2 |
| Application time for the recommendations | 3 months | 17 | 11.9 |
| | 6 months | 20 | 14.0 |
| | 1 year | 19 | 13.3 |
| | 3 years | 27 | 18.9 |
| | Lifelong | 51 | 35.7 |
| | Never applied | 9 | 6.3 |
| Crossing legs | Sometimes | 30 | 21.0 |
| | Usually | 14 | 9.8 |
| | Always | 13 | 9.1 |
| | Never | 86 | 60.1 |
| Squatting | Sometimes | 18 | 12.6 |
| | Usually | 11 | 7.7 |
| | Always | 8 | 5.6 |
| | Never | 106 | 74.1 |
| Sitting cross-legged | Sometimes | 8 | 5.6 |
| | Usually | 8 | 5.6 |
| | Always | 4 | 2.8 |
| | Never | 123 | 86.0 |
| Toilet lift | Sometimes | 17 | 11.9 |
| | Usually | 6 | 4.2 |
| | Always | 11 | 7.7 |
| | Never | 109 | 76.2 |
| European toilet | Sometimes | 2 | 1.4 |
| | Usually | 6 | 4.2 |
| | Always | 123 | 86.0 |
| | Never | 12 | 8.4 |
| Driving | Sometimes | 111 | 77.6 |
| | Usually | 10 | 7.0 |
| | Always | 4 | 2.8 |
| | Never | 18 | 12.6 |
| Cycling | Sometimes | 7 | 4.9 |
| | Usually | 3 | 2.1 |
| | Always | 3 | 2.1 |
| | Never | 130 | 90.9 |
| Running | Sometimes | 22 | 15.4 |
| | Usually | 4 | 2.8 |
| | Always | 2 | 1.4 |
| | Never | 115 | 80.4 |
| Sports | Sometimes | 10 | 7.0 |
| | Usually | 6 | 4.2 |
| | Never | 127 | 88.8 |

THA in a randomized, prospective study with the same follow-up time. This study had only 1 (0.3%) dislocation case overall, which occurred when the patient was transferred from the operating table to the patient bed. The patient belonged to the restricted group and had no operation for instability afterward (9). Both studies reported that the dislocation rate did not increase in the unrestricted patient group. Additionally, the time to return to work and daily activities was shorter in unrestricted patients. However, while the latter study stated that the patients followed in a strict manner, the former study did not specify if the patients followed the restrictions imposed on them adequately. Future studies with longer observation periods, including patient groups with different protocols, would help to determine the role of physician's advice in long-term dislocation rates. Two patients (2%) experienced dislocation in our study, one after 3 weeks and the other 11 months after surgery. Both patients received recommendations from their surgeons and implemented the advice accordingly by 6 and 12 months. The dislocation rate in the present study was similar to previous studies in the literature (10,11). Nonetheless, more patients with hip dislocation were required to analyze the effect of recommendations given after THA.

Most patients followed the recommendations for squatting or sitting cross-legged less frequently, whereas more patients followed the modifications we recommend at home, such as using a seat cushion and a toilet lift. The fact that these movements are relatively simple and more necessary in daily life by patients can be considered as the reason for this situation. On the other hand, there are various studies showing that these recommendations are unnecessary in addition to fundamental restrictions such as adduction, hyperflexion, and rotation above 45 degrees (9,12-14).

Although dislocation remains a crucial complication after THA, there are several surgical precautions (12). Appropriate surgical technique and implant selection and proper placement of components have an critical role in preventing this complication (15). In addition, during the postoperative period, patients' compliance with exercise and recommendations also plays an important role (7,10,16). Furthermore, we argue that modified recommendations by surgeons according to the patients and explaining them clearly would improve patient satisfaction

| Table 3. Comparison of gender and survey responses, n (%) | | | | | |
|---|---|---|---|---|---|
| **Crossing legs** | | | | | |
| | **Sometimes** | **Usually** | **Always** | **Never** | **p*** |
| Female | 25 (24) | 9 (99) | 5 (55) | 65 (63) | **0.017** |
| Male | 5 (13) | 5 (13) | 8 (21) | 21 (54) | |
| **Squatting** | | | | | |
| Female | 10 (9.6) | 7 (6.7) | 4 (3.8) | 83 (79.8) | **0.022** |
| Male | 8 (20.5) | 4 (10.3) | 4 (10.3) | 23 (59.0) | |
| **Driving** | | | | | |
| Female | 92 (88.5) | 1 (1.0) | 0 (0.0) | 11 (10.6) | **0.001** |
| Male | 19 (48.7) | 9 (23.1) | 4 (10.3) | 7 (17.9) | |
| **Running** | | | | | |
| Female | 15 (14.4) | 0 (0.0) | 2(1.9) | 87 (83.7) | **0.007** |
| Male | 7 (17.9) | 4 (10.3) | 0 (0.0) | 28 (71.8) | |
| *Pearson's chi-squared analysis was used | | | | | |

by increasing compliance with the recommendations and reducing the risk of complications.

It was determined that compliance with the recommendations related to sports was the highest. The probable reason for this was that most of the patients were individuals with a relatively high body mass index (the mean number was approximately 31 kg/m$^2$) and a sedentary lifestyle (stated by patients during the interview) before the operation belonged to the elderly population. Considering that these individuals are patients who had tried conservative treatment for a long time before surgery and did not benefit from it, persistent pain that reduces the quality of life can be counted as the reason for staying away from sports (17,18).

This study has shown that women's compliance rates with advice such as crossing legs, squatting, and driving were significantly higher than men's. They were similar in other aspects. A review of literature conducted by Rowan et al. (16) found no difference in the rate of dislocation between women and men. However, we realize that former studies about patient compliance to recommendations after surgery did not investigate the difference between genders (19-21). Nonetheless, as an example, different studies inspecting national data from the USA and Lithuania with numbers of 1,610,155 and 3403 primary THA patients showed that male gender can be a risk factor for dislocation, especially at earlier post-operative period (22,23). We argue that male inattentiveness could be a factor in this difference in genders.

### Study Limitations

Among the limitations of this study, it has shown that a large proportion of the patients did not answer the phone call or did not accept to participate in the survey (55%) (n=177). Due to the nature of the questionnaire, the patients and their relatives may have problems remembering past times; therefore, patient-based bias may have affected the results of this study. The questions asked in the questionnaire were created on the basis of the recommendations of our own clinic. Although there are studies comparing the effect of different restriction protocols on dislocation rates, there is no consensus in the literature regarding the standardization of recommendations after arthroplasty. There is a need for an algorithm in which the results of similar studies can be compared as a reference. Moreover, studies with larger complicated patient series are needed to investigate the effects of recommendations on reducing the risk of dislocation and prosthesis survival.

## Conclusion

This study showed that almost all surgeons give some recommendations to reduce the risk of dislocation after THA. Most patients complied with these recommendations in the early period; however, we observed that compliance decreased over time. Lifelong recommendations may be unnecessary. Moreover, women were more willing than men to comply with the recommendations.

**Ethics Committee Approval:** The study protocol was approved by the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval number: 18, date: 05.01.2023).

**Informed Consent:** Their informed consent was obtained.

**Authorship Contributions:** Surgical and Medical Practices - B.Ç., İ.A.; Concept - B.D., N.R., İ.A.; Design - B.D., M.A., B.Ç.; Data Collection or Processing - N.A., N.R., M.A.; Analysis or Interpretation - B.D., N.A., B.Ç.; Literature Search - N.R., M.A.; Writing - B.D., N.A., İ.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 36-41
**DOI:** 10.4274/imj.galenos.2024.88655

# Risk Factors for Pneumocephalus Following the Surgical Management of Chronic Subdural Hematoma

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## ABSTRACT

**Introduction:** Chronic subdural hematoma is an important type of hemorrhage that can cause morbidity and mortality in older people. The burr hole technique is employed in surgical treatment; however, postoperative pneumocephalus is a common complication of this surgery. To assess factors affecting the postoperative development of pneumocephalus in patients with chronic subdural hematoma.

**Methods:** We analyzed 32 patients who underwent surgical treatment for chronic subdural hematoma using the burr hole technique at our clinic. Baseline and postoperative clinical and radiological data were evaluated. Variables that may affect the development of pneumocephalus, such as age, gender, neurological status, localization of subdural hematoma, thickness, unilaterality or bilaterality, and midline shift, were documented. These variables were analyzed and compared between patients with and without pneumocephalus.

**Results:** The incidence of postoperative pneumocephalus was significantly higher in patients with bilateral hematoma than in those with unilateral hematoma ($p=0.037$; $p<0.05$). There was a significant difference between burr hole localizations among the patients based on the incidence of postoperative pneumocephalus ($p=0.042$; $p<0.05$). The incidence of pneumocephalus was high in patients undergoing surgery using the posterior approach.

**Conclusion:** In the surgical treatment of chronic subdural hematoma, the burr hole technique is considered a safe option because it is effective, minimally invasive, and carries a low risk of complications. However, the occurrence of postoperative pneumocephalus and subsequent recurrent hemorrhage may necessitate reoperation. To prevent the development of pneumocephalus, the burr hole should be created as close to the anterior side as possible.

**Keywords:** Chronic subdural hematoma, hematoma, hemorrhage, pneumocephalus

## Introduction

Chronic subdural hematoma is a significant aspect of neurosurgical practice that can occur spontaneously or because of minor trauma, predominantly affecting older people, and can result in morbidity and mortality (1). These hematomas often arise because of bleeding from subdural bridging veins, which become stretched because of cerebral atrophy (2). Symptomatic and advanced chronic subdural hematomas require surgical treatment. Although it is mostly unilateral, hematomas can occur bilaterally in 8%-35% of patients (3). The burr hole technique, which is often regarded as a minor surgical procedure, is frequently employed in surgical treatment. If necessary, single- or double-sided burr holes can be created. One of the major complications of this surgical technique is pneumocephalus. Pneumocephalus is defined as the presence of air in any intracranial space. It often occurs in small amounts and typically remains asymptomatic. Pneumocephalus can lead to seizures, headaches, irritability, nausea, and dizziness (4,5). In addition, postoperative pneumocephalus following drainage of chronic subdural hemorrhage has been identified as a risk factor for reaccumulation (5-8). Tension pneumocephalus is a rare but life-threatening pathology after intracranial surgical intervention. Tension pneumocephalus occurs when intracranial air is trapped by the check valve system. It behaves like a space-occupying mass and creates an intracranial space that can be life-threatening. Therefore, it must be differentiated from simple pneumocephalus, and its early diagnosis and surgical intervention are crucial.

Although many studies have discussed pneumocephalus and tension pneumocephalus in the context of chronic subdural hematoma, few studies have explored the risk factors. This study presents the risk factors and treatment approaches for pneumocephalus and tension

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**Cite this article as:** Doğu H, Aygün D. Risk Factors for Pneumocephalus Following the Surgical Management of Chronic Subdural Hematoma. İstanbul Med J 2024; 25(1): 36-41.

**Received:** 12.01.2024
**Accepted:** 29.01.2024

pneumocephalus occurring after surgical treatment of chronic subdural hematomas using the burr hole technique.

## Methods

This study retrospectively analyzed patients with chronic subdural hematoma who were surgically treated using the burr hole technique at Atlas University Medicine Hospital between 2006 and 2023.

The study was approved by the Atlas University Non-Invasive Scientific Research Ethics Committee (approval number: 10/10, date: 18.12.2023).

Age, gender, neurological status, history of trauma, duration from trauma to presentation, use of anticoagulants, comorbidities, localization, thickness, unilateral or bilateral occurrence of subdural hematoma, midline shift, recurrence, and pneumocephalus were recorded. All patients underwent preoperative computed tomography (CT) and magnetic resonance imaging (MRI) scans. Cranial CT was performed for postoperative control. Patients with and without postoperative pneumocephalus were compared and analyzed.

Hematomas located anterior and posterior to the coronal suture are called anteriorly and posteriorly localized, respectively. Pre- and postoperative clinical assessments of the patients were conducted using the Markwalder grading system (Table 1).

### Operative Technique

The surgical procedures were performed using patients in the supine position under either general or local anesthesia. The head position was adjusted to the right or left side based on the localization of the hematoma, whereas a neutral head position was maintained in cases of bilateral hematomas. Depending on the localization of the hematomas, 2.5 cm linear incisions were made, followed by subcutaneous dissection and placement of self-retaining retractors. A 1 cm burr hole was created using a drill. The dura was cauterized and then incised. After hematoma flow was observed, the irrigation catheter was advanced into the subdural space. Irrigation was continuously performed with 0.9% saline solution in all directions until sufficient hematoma was aspirated. Irrigation was completed once the irrigation fluid had attained a transparent appearance. In appropriate cases, the pia was opened through a small incision under microscopic visualization. The subdural catheter was inserted, secured to the skin using a suture, and its opposite end was connected to a closed drainage reservoir system. The burr hole was sealed using gel foam. The layers were closed according to their anatomical order.

**Table 1. Neurological grading system of Markwalder et al. (9)**

| |
|---|
| 0: Patient neurologically normal. |
| 1: Patient alert and oriented; mild symptoms, such as headache; absent or mild neurological deficit, such as reflex asymmetry. |
| 2: Patient drowsy or disoriented with variable neurological deficits, such as hemiparesis. |
| 3: Patient stuporous but responding appropriately to noxious stimuli; severe focal signs, such as hemiplegia. |
| 4: Patient comatose with absent motor responses to painful stimuli; decerebrate or decorticate posturing. |

### Postoperative Follow-up

A cranial CT scan was routinely performed on the first postoperative day for control. The drainage was maintained for 2-3 days until hemorrhagic drainage ceased. After removing the catheter, a follow-up CT scan was performed. Patients with stable clinical conditions and no significant problems detected on follow-up cranial CT scans were discharged and followed up through outpatient control visits. After one month, another cranial CT scan was performed for the control. Residual pneumocephalus or subdural hemorrhage was monitored with follow-up CT scans until complete resolution was observed.

### Statistical Analysis

During the evaluation of the study findings, statistical analysis was conducted using the Number Cruncher Statistical System (NCSS) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA). When evaluating the study data, quantitative variables were expressed as mean, standard deviation, median, and minimum and maximum values. Qualitative variables were expressed using descriptive statistics such as frequency and percentage. The Shapiro-Wilk test and box plot graphs were used to assess the fitness of the study data to a normal distribution. Fisher's exact test and Fisher-Freeman-Halton test were employed to compare qualitative data. The results were assessed at a 95% confidence interval, and significance was determined at $p<0.05$.

## Results

The study involved 32 patients, comprising 15 (46.9%) males and 17 (53.1%) females. The patients were aged 38.39-90.00 years, with a mean age of 68.36±16.47 years. Among the patients, 34.4% (n=11) were below 65 years of age, while 68.3% (n=21) were ≥65 years of age. Headache, hemiparesis, imbalance, disturbance of consciousness, speech disturbance, dizziness, and epileptic seizures were reported in 25 (78.12%), 6 (18.75%), 6 (18.75%), 5 (15.62%), 5 (18.75%), 4 (12.50%), and 3 (9.37%) patients, respectively (Table 2).

The rate of postoperative pneumocephalus was not significantly different according to the gender and age of the patients ($p>0.05$). The incidence of postoperative pneumocephalus was significantly higher in patients with bilateral hematoma than in those with unilateral hematoma ($p=0.037$; $p<0.05$).

There was a statistically significant difference between the burr hole positions of the patients according to the occurrence of postoperative pneumocephalus ($p=0.042$; $p<0.05$). The incidence of pneumocephalus was higher in patients undergoing intervention using a posterior approach. The incidence of pneumocephalus was not significantly different according to hematoma thickness, shift measurements, and pre-operative and postoperative clinical grades ($p>0.05$) (Table 3).

There was no mortality in this study, and recurrence of chronic subdural hematoma was observed in two patients (6.25%). Postoperative pneumocephalus was in both recurrent cases. The recurrent patients underwent drainage surgery using a burr hole, and subsequent postoperative follow-up revealed the disappearance of both the hematoma and pneumocephalus, with no observed neurological deficits. No postoperative seizures were observed as complications. Antiepileptic

**Table 2. Distribution of descriptive characteristics**

| | | n (%) |
|---|---|---|
| Gender | Male | 15-46.9 |
| | Female | 17-53.1 |
| Age | Mean ± SD | 68.36±16.47 |
| | Median (min.-max.) | 75.14 (38.39-90) |
| | <65 years | 11-34.4 |
| | ≥65 years | 21-65.6 |
| Unilateral or bilateral hematoma | Unileteral | 24-75.0 |
| | Bilateral | 8-25.0 |
| Hematoma side | Right | 10-31.3 |
| | Left | 14-43.8 |
| | Bilateral | 8-25.0 |
| Burr-hole position | Anterior | 6-18.8 |
| | Posterior | 6-18.8 |
| | Anterior + posterior | 20-62.5 |
| Interval between trauma and surgery (months) | Mean ± SD | 2.44±0.85 |
| | Median (min.-max.) | 3 (1-4) |
| Cause of trauma (n=16) | Falling | 11-68.8 |
| | Impact | 4-25.0 |
| | Traffic accident | 1-6.3 |
| Use of anticoagulants | No | 25-78.1 |
| | Yes | 7-21.9 |
| Additional disease | HT | 10-58.8 |
| | DM | 6-35.3 |
| | Other | 8-47.1 |
| Hematoma thickness (cm) | 1-2 cm | 18-56.3 |
| | >2 cm | 14-43.8 |
| Midline shift (mm) | <5 mm | 20-62.5 |
| | ≥5 mm | 12-37.5 |
| Postoperative pneumocephalus | No | 16-50.0 |
| | Yes | 16-50.0 |
| Length of hospital stay (days) | Mean ± SD | 5.69±2.39 |
| | Median (min.-max.) | 5-3-12 |
| Pre-op. grade (Markwalder) | Grade 1 | 10-31.3 |
| | Grade 2 | 19-59.4 |
| | ≥ Grade 3 | 3-9.4 |
| Postop. grade (Markwalder) | Grade 0 | 15-46.9 |
| | Grade 1 | 14-43.8 |
| | ≥ Grade 2 | 3-9.4 |

SD: Standard deviation, min.: Minimum, max.: Maximum, HT: Hypertension, DM: Diabetes mellitus, preop: Preoperative, postop: Postoperative

therapy was started in patients who experienced preoperative epileptic seizures and was maintained for a minimum duration of six months.

Postoperatively, tension pneumocephalus occurred in two (6.25%) patients, who were described as follows:

**Case 1:** A 75-year-old male hypertensive patient presented to the emergency department with complaints of headache, weakness, nausea, and vomiting but had no neurological deficit. Cranial CT and

**Table 3. Comparison of descriptive characteristics according to the occurrence of pneumocephalus**

| Absent, (n=16) | | Pneumocephalus | | p |
|---|---|---|---|---|
| | | Present, (n=16) | | |
| Gender | Male | 9-56.3 | 6-37.5 | **0.288**[a] |
| | Female | 7-43.8 | 10-62.5 | |
| Age | <65 years | 5-31.3 | 6-37.5 | **0.710**[a] |
| | ≥65 years | 11-68.8 | 10-62.5 | |
| Unilateral or bilateral hematoma | Unileteral | 15-93.8 | 9-56.3 | **0.037**[b] |
| | Bilateral | 1-6.3 | 7-43.8 | |
| Burr-hole position | Anterior | 6-37.5 | 0-0 | **0.042**[c] |
| | Posterior | 2-12.5 | 4-25.0 | |
| | Ant. + post. | 8-50.0 | 12-75.0 | |
| Hematoma thickness (cm) | 1-2 cm | 10-62.5 | 8-50.0 | **0.476**[a] |
| | >2 cm | 6-37.5 | 8-50.0 | |
| Midline shift (mm) | <5 mm | 11-68.8 | 9-56.3 | **0.465**[a] |
| | ≥5 mm | 5-31.3 | 7-43.8 | |
| Preoperative grade (Markwalder) | Grade 1 | 7-43.8 | 3-18.8 | **0.201**[c] |
| | Grade 2 | 7-43.8 | 12 (75) | |
| | ≥ Grade 3 | 2-12.5 | 1-6.3 | |
| Postoperative grade (Markwalder) | Grade 0 | 9-56.3 | 6-37.5 | **0.436**[c] |
| | Grade 1 | 5-31.3 | 9-56.3 | |
| | ≥ Grade 2 | 2-12.5 | 1-6.3 | |

[a]Pearson's chi-square test, [b]Fisher's exact test, [c]Fisher-Freeman-Halton test, p<0.05

MRI revealed bilateral chronic subdural hematoma with a thickness of 1.8 cm at its widest point (Figure 1). It was discovered that the patient had experienced mild head trauma from a fall two months earlier. The patient underwent subdural hematoma drainage with bilateral anterior and posterior burr holes under general anesthesia. The operation proceeded without any complications, and the patient experienced regression of headaches and other complaints during the early postoperative period, which was uneventful. On the second postoperative day, the patient began exhibiting signs of altered consciousness and agitation. Control CT scans revealed massive subdural pneumocephalus along with the Mount Fuji sign (Figure 2). The patient underwent a reoperation, during which the burr hole incision site was reopened. Air was aspirated during the procedure. The subdural space was filled with saline solution. A catheter was inserted. Two hours after surgery, the patient's agitation and changes in consciousness started to regress. The follow-up cranial CT scan indicated a reduction in pneumocephalus (Figure 3). The catheter was removed on day 3. Follow-up cranial CT scans with intervals revealed a gradual reduction in pneumocephalus. By day 30, the cranial CT scan showed complete disappearance of pneumocephalus, with no remaining hematoma (Figure 4). The patient was scheduled for follow-up at the outpatient clinic without neurological deficits.

**Case 2:** A 78-year-old man with diabetes mellitus and hypertension presented to the emergency room with headache and confusion. Cranial CT revealed a chronic subdural hematoma, measuring 2.5 cm at its widest point, located in the right frontoparietal region. A burr hole was created in the right frontoparietal region, and the hematoma

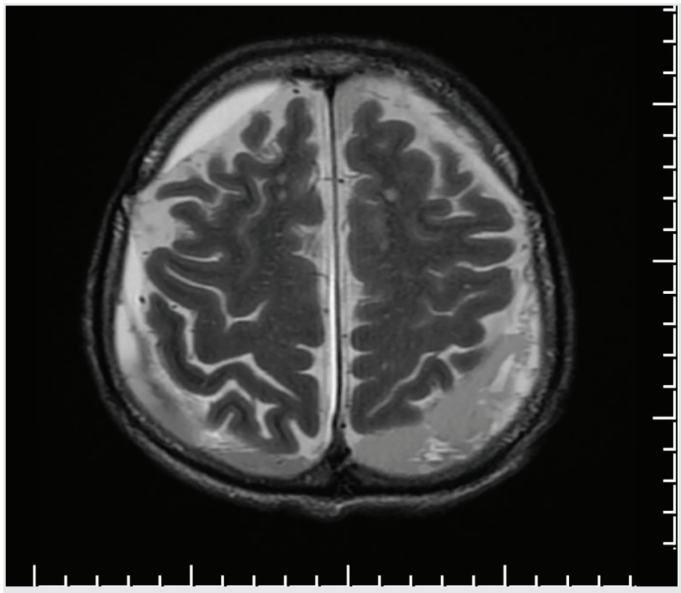

**Figure 1.** Preoperative axial T2-weighted cranial magnetic resonance imaging reveals chronic hematoma with a thickness of 1.5 cm at its widest point in both subdural spaces

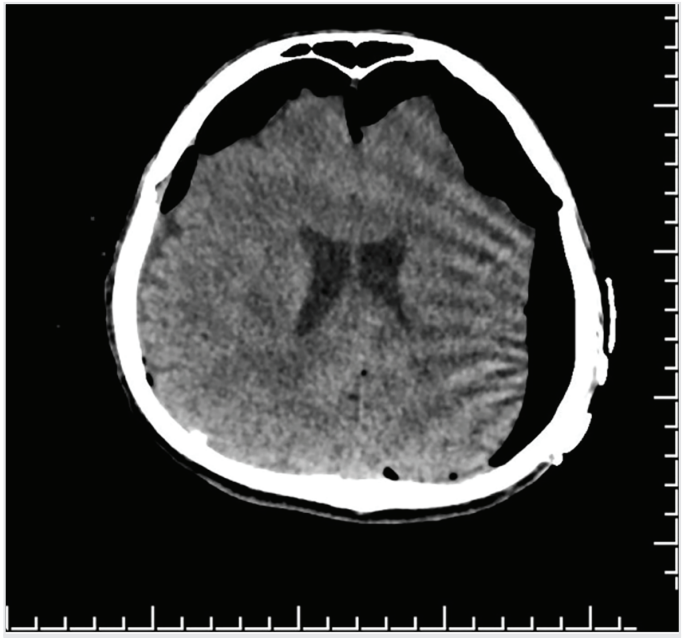

**Figure 2.** Postoperative axial computed tomography imaging in the parenchymal window after the burr hole technique for the evacuation of subdural hematoma. Widespread air densities consistent with pneumocephalus were observed in the subdural space. The Mount Fuji sign is in the left frontal region

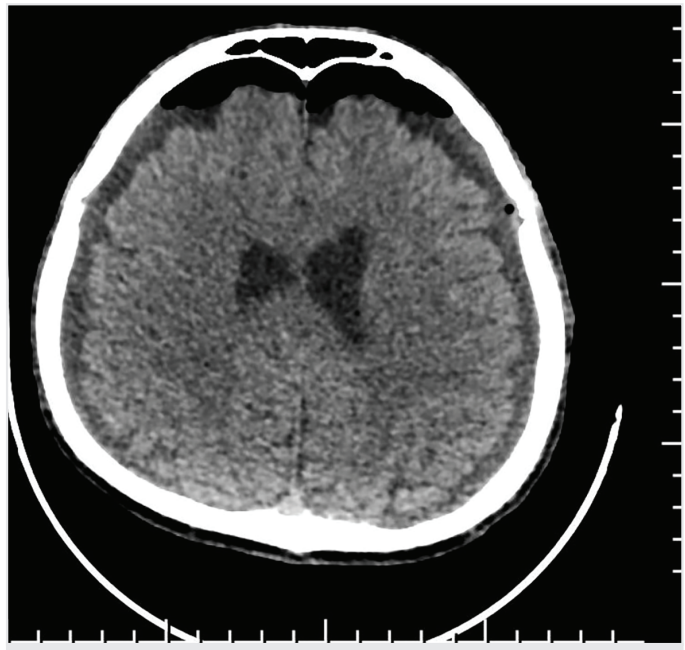

**Figure 3.** During the second surgery, air aspiration was performed, and the subdural space was filled with physiological saline solution. Postoperative axial computed tomography imaging in the parenchymal window revealed reduced pneumocephalus in both subdural spaces. Air densities secondary to the operation are in both frontal regions

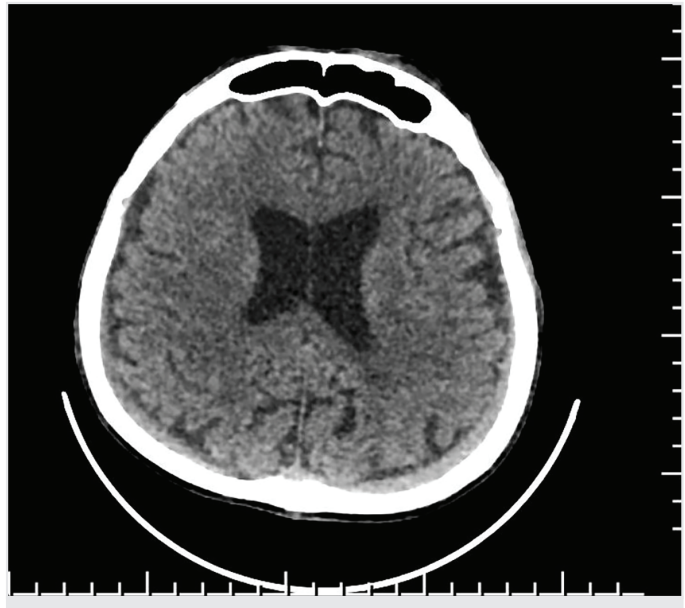

**Figure 4.** Axial computed tomography imaging in the parenchymal window 1 month after the second surgery. It is observed that the subdural collection and air densities regressed

was drained. The state of confusion improved during the postoperative period, and the hematoma showed regression in the follow-up cranial CT scan. The catheter was removed on the third day. However, on the fourth day, the patient developed headache and confusion, prompting a repeat cranial CT scan. Cranial CT revealed subdural pneumocephalus and a 3 mm midline shift in the same location. Upon making the skin incision, pressurized air was observed emanating from the subdural space. It was considered that air might have been drawn through the hole in the skin after the catheter was withdrawn. The subdural space was filled with saline solution, followed by the insertion of a catheter. During follow-up, both pneumocephalus and hemorrhage had resolved on cranial CT scan, and no neurological deficits were observed.

## Discussion

The development of cavities within the cranial subdural space due to atrophy in advanced ages may increase the susceptibility to the development of chronic hemorrhage. Similarly, the surgical treatment

of chronic subdural hematoma using the burr hole technique may lead to the development of pneumocephalus and recurrent hemorrhage within the subdural space in the postoperative period. Postoperative simple pneumocephalus can occur after burr hole evacuation of chronic subdural hematoma. It is often asymptomatic because it does not exert significant pressure or compression, generally not necessitating treatment unless it remains asymptomatic. Reports have indicated its resorption and eventual disappearance within days to weeks (10,11). However, it can sometimes be symptomatic or cause recurrent hemorrhage (4-6,12).

It has been reported in the literature that the recurrence rates following surgical treatment of subdural hematoma range from 10% to 33% (5). To prevent recurrence, some authors advocate the placement of a subperiosteal catheter between the calvarium and periosteum rather than a subdural catheter. Therefore, they observed no damage to the neural parenchyma or bridging veins and reported a reduced recurrence rate (13,14). One of the most important causes of recurrence is believed to be the development of postoperative pneumocephalus (10). Postoperative pneumocephalus leads to recurrence through various mechanisms. Pneumocephalus within the subdural space induces negative pressure, resulting in the reaccumulation of blood (15). According to You and Zheng (5) air bubbles are displaced by the movement of the patient and cause rupture of the bridging veins and rebleeding. Therefore, although postoperative pneumocephalus is usually asymptomatic, it contributes to recurrence and significantly influences the outcome of surgical treatment for chronic subdural hematoma.

The incidence of pneumocephalus in the early postoperative phase ranges between 14% and 44% (16,17). However, in our series, this rate was observed to be 50%. We believe that the high rate of pneumocephalus was due to the inclusion of patients with a small volume of pneumocephalus. Various reasons for developing pneumocephalus have been reported. Dobran et al. (18) and You and Zheng (5) emphasized the importance of creating the burr hole at the highest point possible by properly positioning the patient during the intervention. They also reported that air entering through the burr hole during surgery could ascend to the upper parts of the subdural space and become trapped there (5,18). In our study, pneumocephalus was more common in patients undergoing surgery using a posterior approach. The hemorrhagic cerebrospinal fluid within the subdural space drains out because of its fluidity and the force of gravity, allowing air to enter and substitute for the hemorrhagic cerebrospinal fluid. Furthermore, insufficient head rotation in patients with bilateral hematomas poses an increased risk, particularly when both anterior and posterior burr holes are opened. This allows fluid to drain from the lower burr hole while allowing air to enter through the upper burr hole. To prevent air from entering the subdural space around the catheter, during catheter advancement and initiation of irrigation to drain the hemorrhage, the potential air entry site in the burr hole must be covered with materials such as gel foam.

The authors have devised various surgical strategies to prevent the development of postoperative pneumocephalus. In their study, Chavakula et al. (15) conducted hematoma evacuation through a 3 cm craniotomy. They then inserted a catheter and aspirated air from the catheter using a syringe. This method facilitates brain expansion and decreases the incidence of pneumocephalus and subsequent recurrence (15).

Some authors have proposed an alternative method for preventing pneumocephalus by precisely determining the localization of the inserted subdural catheter. Nakaguchi et al. (19) reported in a study involving 63 patients that the position of the subdural catheter tip influenced the occurrence of postoperative pneumocephalus. They demonstrated that occipital and parietal catheters resulted in a higher incidence of pneumocephalus than frontal catheters. Cecchini (20) used two subdural drainage catheters in their study. They reported that pneumocephalus can be prevented by using one catheter for irrigation and the other for air aspiration. Zakaraia et al. (16) and Erol et al. (1) conducted completely different studies. In their study, one group of patients underwent irrigation, whereas the other group did not receive irrigation. They reported that pneumocephalus was less frequent in cases where irrigation was not used.

After surgical treatment of chronic subdural hematoma using the burr hole technique, there exists a risk of tension pneumocephalus, a condition less frequent than simple pneumocephalus but characterized by a distinct clinical course. The mechanism of tension pneumocephalus involves a valve system that permits air to enter but inhibits its release. This initiates a process that results in gradual neurological deterioration, necessitating urgent intervention.

In the literature, the risk of developing tension pneumocephalus after treatment of chronic subdural hematoma using the burr hole technique has been reported to range from 2.5% to 16% (21). In our series, tension pneumocephalus occurred in two patients (6.25%). There is no clear information in the literature regarding the causes and prevention of tension pneumocephalus. In our first case, we believe that the hemorrhagic cerebrospinal fluid drained through the catheter placed in the posterior burr hole, yet a substantial volume of air remained within the space. In our series, we noticed a higher incidence of pneumocephalus in relation to the burr holes created to evacuate posterior hematomas. To prevent this occurrence, we suggest placing the burr hole as high as possible and extending the catheter frontally. We believe that this approach will allow the drainage of potential subdural air because it will be situated at the top when the patient is placed in the supine position, while positioning the fluid advantageously at the bottom. Otherwise, after the drainage of hemorrhagic cerebrospinal fluid, the catheter may allow the entry of air after draining the fluid. In the second case in this study, we believe that upon catheter withdrawal, air might have been drawn through the catheter site opening, leading to the development of tension pneumocephalus. To prevent this from happening in subsequent patients, a gel was applied to both the catheter exit site and the incision site after catheter removal, aiming to prevent the entry of air.

**Study Limitations**

This study is a retrospective analysis conducted at a single center and may be limited because of the small number of cases. A multicenter prospective study with a larger number of patients can be conducted.

## Conclusion

The burr hole technique is a safe, effective, and minimally invasive option for the surgical treatment of chronic subdural hematoma, offering a low risk of complications. However, postoperative complications associated with this technique, such as pneumocephalus and recurrent hemorrhage, may necessitate repeat surgical intervention. In addition, these complications might extend the duration of hospitalization. During the use of this technique, positioning the burr hole as close to the anterior region as possible can decrease the risk of pneumocephalus development.

**Ethics Committee Approval:** The study was approved by the Atlas University Non-Invasive Scientific Research Ethics Committee (approval number: 10/10, date: 18.12.2023).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Surgical and Medical Practices - H.D.; Concept - H.D.; Design - H.D.; Data Collection or Processing - H.D.; Analysis or Interpretation - H.D., D.A.; Literature Search - H.D., D.A.; Writing - H.D., D.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 42-8
**DOI:** 10.4274/imj.galenos.2024.91074

# Ensuring Corpectomy and Stabilization Effectiveness in Patients Who Underwent Single Posterior Approaches

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## ABSTRACT

**Introduction:** Today, approximately 2 million people worldwide suffer from spinal tuberculosis (STB). In endemic areas, classical STB is often accompanied by spondylodiscitis.

**Methods:** This study retrospectively analyzed 15 patients diagnosed with STB who were followed up in our clinic from January 2010 to August 2021. The study included a total of 15 patients diagnosed with spondylodiscitis, 7 males and 8 females, with detection of STB bacillus (6 patients) and/or pathological diagnosis of caseous necrosis (15 patients).

**Results:** Pre-operative neurological examinations of the patients revealed neurological deficits according to the Frankel scale, except in 2 patients. According to the Frankel scale, 8 patients showed improvement, 6 of them did not change, 1 worsened, and 13 had fusion documented on radiological imaging.

**Conclusion:** Anterior corpectomy and posterior instrumentation may be a safe and effective technique compared with all other surgical interventions applicable in such patients.

**Keywords:** Thoracic and lumbar Pott's disease, posterior surgical treatment, anterior corpectomy

## Introduction

Spinal tuberculosis (STB) is one of the oldest diseases known to exist in humans, documented in Egyptian mummies dating back 5000 years. The first STB case was presented by Percival Pott in 1779 (1). Today, STB disease continues to be seen worldwide despite the developments in good nutrition, easy access to doctors, and treatment procedures. In endemic areas, classical TB is often accompanied by spondylodiscitis. With the recent increase in multidrug resistance in TB, the clinical presentation and treatment modalities have become very complex (2).

Pott's disease is clinically manifested by spinal deformity, mechanical instability, and neurological deficit, and surgical procedures may become mandatory in STBs that do not respond to drug therapy. These interventions range from radiology-assisted abscess drainage to open decompression and restoration (3).

This study presents the clinical, radiological imaging and surgical outcomes of a series of 15 consecutive patients with thoracic or lumbar spondylodiscitis requiring open surgery despite all medical treatment, who underwent debridement including spondylectomy as well as transpedicular posterior stabilization using the posterior approach without anterior opening (lumbotomy/thoracotomy) and aims to convey our experiences in this process.

## Methods

The study was approved by the Sakarya University Local Ethical Committee (approval number: E-71522473-050.01.04-92657-570, date: 03.01.2022).

In this study, 15 patients diagnosed with STB based on radiological examination, laboratory tests, and histopathology between January 2010 and August 2021 were retrospectively analyzed.

A total of 15 patients diagnosed with spondylodiscitis, 7 (46.6%) males and 8 (53.4%) females, with detection of TB bacillus (6 patients, 40%) and/or pathological diagnosis of caseous necrosis (15 patients, 100%), were included in the study (Patients with abscess formation on the anterior of the vertebral body far from the site of spondylodiscitis were excluded from the study). Patients' age was 54.6±16.60 (standard deviation).

Demographic distribution, predisposition status, clinical manifestation, comorbidities, microbiological and histopathological diagnoses, and clinical and radiological outcomes of the patients were retrospectively reviewed. The mean follow-up period in our study group was 20.4 months (6-108 months) (Table 1).

Patients with neurological deficits were classified according to the Frankel scale (Table 2) (4).

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**Cite this article as:** Kaya M, Ceylan D. Ensuring Corpectomy and Stabilization Effectiveness in Patients Who Underwent Single Posterior Approaches. İstanbul Med J 2024; 25(1): 42-8.

**Received:** 11.11.2023
**Accepted:** 30.01.2024

**Table 1. Length of follow-up, pre-operative and end of follow-up Frankel grades, and surgical procedures in 15 patients**

| Patient no, (n=15) | Age, (mean ± SD): 54.6±16.60 | Diagnosis | Sedimentation, (mean ± SD): 23.53±17.58 | CRP, (mean ± SD): 17.86±25.57 | Frankel pre-op | Frankel post-op | Follow-up time, (months) | Pre-op-VAS, (mean ± SD): 7.8±0.83 | Post-op-VAS (2. month), (mean ± SD): 2.93±0.79 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 31 | T6 Pott | 8 | 2 | D | E | 108 | 8 | 3 |
| 2 | 28 | T5 Pott | 13 | 3 | E | E | 16 | 7 | 3 |
| 3 | 63 | T8-9 Pott | 47 | 35 | D | E | 19 | 8 | 2 |
| 4 | 50 | T2 Fracture | 6 | 3 | E | E | 15 | 7 | 3 |
| 5 | 64 | T5 Pott | 20 | 13 | C | C | 6 | 8 | 3 |
| 6 | 53 | T5 Discitis | 70 | 103 | C | A | Died* | 9 | 3 |
| 7 | 70 | L2-3 Discitis | 6 | 3 | D | E | 13 | 7 | 2 |
| 8 | 70 | T11 Pott | 13 | 8 | D | E | 19 | 7 | 3 |
| 9 | 21 | L1 Pott | 16 | 9 | D | E | 21 | 7 | 2 |
| 10 | 50 | T12 Pott | 12 | 11 | A | A | 24 | 8 | 3 |
| 11 | 69 | T7-8 Pott | 40 | 10 | A | A | 8 | 7 | 2 |
| 12 | 47 | L1 Pott | 30 | 29 | D | E | 6 | 9 | 5 |
| 13 | 65 | L2 Pott | 28 | 23 | D | E | 12 | 8 | 3 |
| 14 | 69 | L2 Pott | 22 | 13 | D | E | 9 | 9 | 3 |
| 15 | 69 | T7-8 Pott | 22 | 3 | A | A | 9 | 9 | 4 |

SD: Standard deviation, CRP: C-reactive protein, Pre-op-VAS: Pre-operative-visual analog scale, Post-op-VAS: Post-operative-visual analog scale score was significantly decreased compared with the pre-operative value ($p<0.001$). *The patient died on the 15th post-operative day because of cardiac problems

**Table 2. Frankel classification of neurological lesions**

| Grade | Frankel scale |
|---|---|
| Grade A | Complete neurological injury: below injury, no motor or sensory function |
| Grade B | Preserved sensory sensation only - no motor function below injury; partial sensory function below injury |
| Grade C | Non-functional preserved motor function: there is practically unused motor function below the injury |
| Grade D | Preserved motor function: below injury there are motor function able to walk with assistance but strength not normal |
| Grade E | Normal motor - normal sensory motor and sphincter function may have abnormal reflexes and subjective sensory problems |

Pre-operative and post-operative white blood cell count (WBC) [men mean: 9.64 mcL (6.8-16), women mean: 8.11 mcL (6.4-16)], erythrocyte sedimentation rate (ESR) [men: 16 mm/h (6-47), women: 28.97 mm/h (6-70)] and C-reactive protein (CRP) [men: 11.67 (2.7-35) mg/L, women: 11.17 (2.6-40) mg/L] levels of each patient were recorded (Table 3).

All patients were evaluated pre-operatively and post-operatively using bilateral spinal anteroposterior and lateral radiographs, computed tomography (CT), and magnetic resonance imaging (MRI).

The criteria for deciding on the indication for surgery in patients were non-response to treatment despite active treatment of STB (insignificant decrease in sedimentation and CRP, severe pain), destruction of the vertebrae and discs causing instability, increase in kyphosis-spine malalignment, presence or risk of neurologic deficit, and abscess formation.

All patients were administered prophylactic antibiotics (cefazolin 1000 mg IV) pre-operatively, and posterior transpedicular corpectomy and cage were stabilized with posterior transpedicular screw systems in the same session in all patients included in the study. During the pre-operative period, the cartilage endplate of the affected spine and disc was removed up to the healthy bleeding corpus bone, and adequate decompression of the dural sac was achieved. In all patients, debridement was performed as much as possible, and in the presence of abscess formation, abscess drainage was performed in the same session as possible.

During surgery, at least 4 samples were taken from the infective site of all cases for simultaneous culture (Gram-staining, aerobic and anaerobic culture and susceptibility tests, fungal culture, TB appropriate cultures) and histopathological examination.

**Table 3. Pre-operative and post-operative total acute phase reactants results**

| (n=15) | Pre-op and post-op-WBC | Pre-op and post-op ESR | Pre-op and post-op CRP |
|---|---|---|---|
| Men, (n=7) | 9.64 mcL (mean ± SD; 6.8-16 mcL) | 16 mm/h (mean ± SD; 6-47 mm/h) | 11.67 mg/L (mean ± SD; 2.7-35 mg/L) |
| Women, (n=8) | 8.11 mcL (mean ± SD; 6.4-16 mcL) | 28.97 mm/h (mean ± SD; 6-70 mm/h) | 11.17 mg/L (mean ± SD; 2.6-40 mg/L) |

WBC: White blood cells, ESR: Erytrocyte sedimentation rate, CRP: C-reactive protein, SD: Standard deviation

Fusion criteria on multi-planar recon wereas follows: (1) presence of bony trabeculation and (2) presence or lack of bony lucency at the iliac bone graft/vertebral body interface (4).

## Results

Of the patients included in the study, 8 (53.4%) were female and 7 (46.6%) were male. The mean ages were 52.71 (21-70) in females and 56.25 (50-69) in males, and the mean year of the group was 54, while the mean age was 58. There were 3 patients [male (M): 2/female (F): 1] between the ages of 21-39, 4 patients between the ages of 40-59 (F: 3/M: 1), 7 patients aged 60 and above (M: 3/F: 4) (Table 1).

### Clinical Presentation

A total of 19 vertebral corpus involvements were detected in the patients included in the study. Of the patients, 11 (73.3%) had single-level involvement and 4 (26.6%) had two-level involvement. In the study group, 10 (66.6%) patients had thoracic involvement and 5 (33.3%) patients had lumbar involvement. The most frequently affected vertebrae level was T8, which was involved in 3 patients (20%). In this group, 6 patients (40%) had abscess formation in the soft tissue adjacent to the paravertebral or psoas muscle. The time from the onset of symptoms to diagnosis was approximately 19.75 months (ranged between 1-108 months) (Table 1).

All 15 patients (100%) had local spine pain, and 5 (33%) had additional radicular pain. Radicular pain was unilateral in 3 patients and bilateral in 2 patients. Of the patients, 4 (26.7%) were Frankel A, 1 (6.6%) was Frankel C, and 10 (66.6%) were Frankel E.

In the entire study group, 11 (73%) patients had a poor general condition due to comorbidities. Some of our patients were receiving treatment for the following diagnoses: diabetes mellitus (DM) type 2 and hypertension (HT) (3 patients, 20%), DM type 2 (2 patients, 13%), chronic renal failure (CRF) and HT (2 patients, 13%), CRF (1 patient, 6%), DM type 2, HT and chronic obstructive pulmonary disease (1 patient, 6%), hypothyroidism (1 patient, 6%), 1 had thyroid cancer and Goiter (1 patient, 6%).

### Laboratory Results

Pre-operative and post-operative WBC [men mean: 9.64 mcL (6.8-16), women mean: 8.11 mcL (6.4-16)], ESR [men: 16 mm/h (6-47), women: 28.97 mm/h (6-70)], and CRP [men: 11.67 (2.7-35) mg/L, women: 11.67 (2.7-35)] levels of each patient were recorded.

### Diagnostic Imaging

STB-specific bone and intervertebral space destructions were observed on bilateral spinal radiographs. Early-stage disc space deterioration and endplate erosion were observed in 4 patients (26.6%), and vertebral corpus damage was observed in 11 (73.3%) patients. Spinal CT scans of 6 (40%) patients revealed collapse of the vertebral corpus, destruction, abscess in the paravertebral and/or psoas region, and spinal cord or dural sac compression due to abscess and bone destruction (Figure 1a). The pre-operative T1W-weighted sagittal and axial MRI of the spine in Figure 1b show bone destruction from the T7 to T8 vertebrae, disc involvement, epidural abscess, and spinal cord compression (Figure 1a, b).

### Surgery

In the late stage of STB, clinically painful deformities and progressive neurological deficits occur. The radiological and clinical findings we determined for surgical indication were kyphosis, persistent low back pain, inability to lie in the supine position, and progressive neurological deficits.

In the study group, 10 (66.6%) patients underwent single-level discectomy, corpectomy, and instrumentation, and 5 (33.3%) patients underwent two-level discectomy, corpectomy, and instrumentation. The details of the surgical procedures are given in Table 4.

### Patients' Operative and Post-Operative Data

In our study group, the mean blood loss of patients was 630 mL [range: 350-1100 mL (Table 5)], the mean surgical time was 220 min (range: 170-250 min), pre-operative visual analogue scale (VAS) was 7.7% (7-9), and post-operative VAS was 2.8 (2-3), resulting in a 100% reduction in VAS (Table 5). The average length of hospitalization was 13.1 days (6-54 days), and neurological improvement was observed in 88.8% of patients who were not Frankel scale A (Table 1).

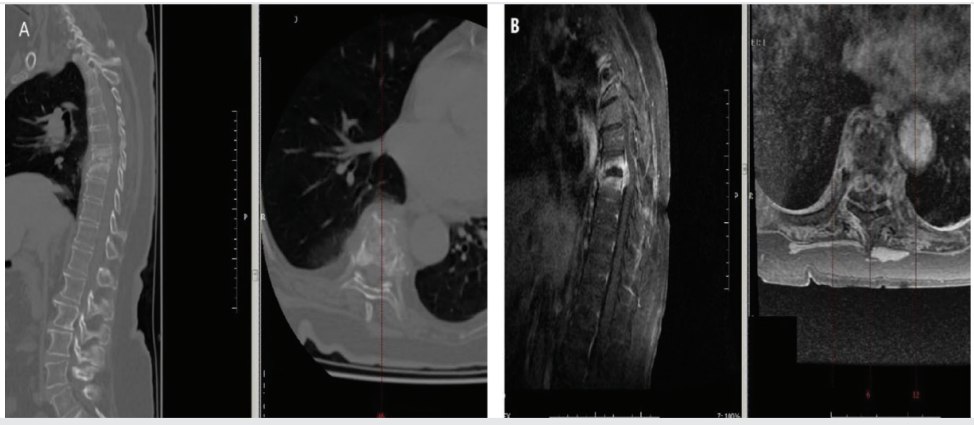


**Figure 1.** (a) Multi-planar recon in sagittal and axial planes showing T7-8 disc space collapse and T7-8 vertebral corpus destruction (white arrow). (b) Contrast-enhanced magnetic resonance imaging in sagittal and axial planes showing T7-8 compression fractures, T7-8 vertebral corpuses posterior to the epidural space, hyperintense lesion with wide contrast suppressing the spinal cord in T1W sequences, and intense contrast enhancement in T7-8 vertebral corpuses (blue arrow)

**Table 4. Surgical procedures performed on patients**

| Patient no. | Surgical procedures |
|---|---|
| 1 | T4-5-8 posterior stabilization, T6 corpectomy, T5-7 cage |
| 2 | T3-4-6-7-8 posterior stabilization, T5 corpectomy, T4-6 cage |
| 3 | T5-6-7-10-11-12 posterior stabilization, T8-9 corpectomy, T7-10 cage |
| 4 | C7-T1-T3-4-5 posterior stabilization, T2 corpectomy, T1-3 cage |
| 5 | T2-3-4-7-8-9 posterior stabilization, T6 corpectomy, T4-7 cage |
| 6 | T2-3-6-7 posterior stabilization T4-5 corpectomy, T3-6 cage |
| 7 | T12-L1-3-4 posterior stabilization, L2 corpectomy, L1-3 cage |
| 8 | T7-8-9-12-L1 posterior stabilization, T10 corpectomy, T9-11 cage |
| 9 | T9-10-11-L2-3-4 posterior stabilization, L1 corpectomy, T12-L2 cage |
| 10 | T10-11-L1-2 posterior stabilization, T12 corpectomy, T11–L1 cage |
| 11 | T54-5-6-9-10-11-12 posterior stabilization, T7-8 corpectomy, T6-9 cage |
| 12 | T10-11-12-L3-4 posterior stabilization, L1 corpectomy, T12–L1 Fibula Greft |
| 13 | T12-L1-3-4 posterior stabilization, L2 corpectomy, L1-3 cage |
| 14 | T12-L1-3-4 posterior stabilization, L2 corpectomy, L1-3 cage |
| 15 | T4-5-6-9-10-11 posterior stabilization, T7-8 corpectomy, T6-9 cage |

**Table 5. Surgical time, peroperative amount of bleeding, pathology, and microbiology results**

| Patient no. | Surgical time (minutes) | Peroperative amount of bleeding (mL) | Pathology | Microbiology |
|---|---|---|---|---|
| 1 | 210 | 550 | Granulomatous lesion | Culture negative |
| 2 | 205 | 600 | Granulomatous lesion | Culture negative |
| 3 | 270 | 800 | Granulomatous lesion | Culture negative |
| 4 | 170 | 350 | Granulomatous lesion | Culture negative |
| 5 | 200 | 450 | Granulomatous lesion | Culture negative |
| 6 | 250 | 700 | Granulomatous lesion | Culture negative |
| 7 | 170 | 500 | Granulomatous lesion | Culture negative |
| 8 | 220 | 550 | Granulomatous lesion | Culture negative |
| 9 | 200 | 480 | Granulomatous lesion | *M. Tuberculosis* positive |
| 10 | 215 | 550 | Granulomatous lesion | *M. Tuberculosis* positive |
| 11 | 185 | 1100 | Granulomatous lesion | Culture negative |
| 12 | 190 | 770 | Granulomatous lesion | *M. Tuberculosis* positive |
| 13 | 175 | 800 | Granulomatous lesion | *M. Tuberculosis* positive |
| 14 | 180 | 700 | Granulomatous lesion | *M. Tuberculosis* positive |
| 15 | 200 | 810 | Granulomatous lesion | *M.Tuberculosis* Positive |

### Complications

One of our patients died on the 15th day because of poor general of and multi-organ failure. Two patients (13.3%) had wound infections due to chronic diseases, and one patient had pseudoarthrosis in screws. They were treated with appropriate medical treatment.

### Clinical Outcomes

Pre-operative neurological examinations of the patients revealed neurological deficits according to the Frankel scale, except in 2 patients (13.3%). According to the Frankel scale, 8 (53.3%) showed improvement, 6 (40%) did not change, and 1 (0.6%) worsened (Table 1).

### Radiographic Outcomes

During follow-up, radiological imaging was performed in all patients (Table 1). Fusion was documented in 13 (86%) patients. No instrumentation errors, loosening, fractures, or complications related to the corpectomy cage were observed in any of the patients during follow-up.

### Statistical Analysis

Initially, the normality of all variables was evaluated. Means and frequencies were assessed for continuous and categorical variables, respectively.

### Sample Case

A 69-year-old female patient who was admitted to the hospital with back pain and inability to walk in November 2020 had a VAS score of 8 and reported fatigue and night sweats. Below the T8 distance, the motor examination outcome was 1/5, sensory examination was anesthetic, and deep tendone reflexes were hypoactive. The patient had HT.

Pre-operative diagnostic tests of the patient revealed standard CRP (3.02 mg/dL, N: 0-5 mg/dL), procalcitonin (0.049 ng/mL, N: 0-0.5 ng/mL), and ESR (12 mm/h, N: 0-30 mm/h) rates. MRI revealed defects in the T7-8 corpus, abscesses in the T7-8 disc and epidural space, inflammation, and granulation reaction of the dura and disc surfaces at the T7-8 level. Intense contrast enhancement at the T7-8 distance was evaluated as compatible with spondylodiscitis. Pre-operative blood culture was obtained from the patient. Mycobacterium tuberculosis appeared in blood cultures. Antituberculosis drugs, Isoniazid 300 mg/day, rifampicin 600 mg/day, etambutol 1500 mg/day, and pyrazinamide 2000 mg/day were started by the infectious diseases department.

T4-5-6-9-10-11 stabilization, T7-8 total corpectomy, and tumor cage fusion surgery were performed in the patient with a posterior approach. Peroperative culture and pathology samples were taken (Figures 2a-d, 3a, b).

The patient's peroperative blood culture was also positive for Mycobacterium tuberculosis. At the 2nd post-operative week, the pathology result was compatible with a granulomatous lesion (Table 4). Physiotherapy was started in the 3rd week. However, there was no change in the motor examination after 2 months of treatment. At the end of the 2nd month, VAS was 3. At the end of the 2nd month, ethambutol and pyrazinamide were discontinued. Maintenance treatment was completed in 7 months with the dual antituberculosis drugs isoniazid (300 mg/day) and rifampicin (600 mg/day). At the end of 9 months of anti- tuberculosis treatment, cure treatment was given.

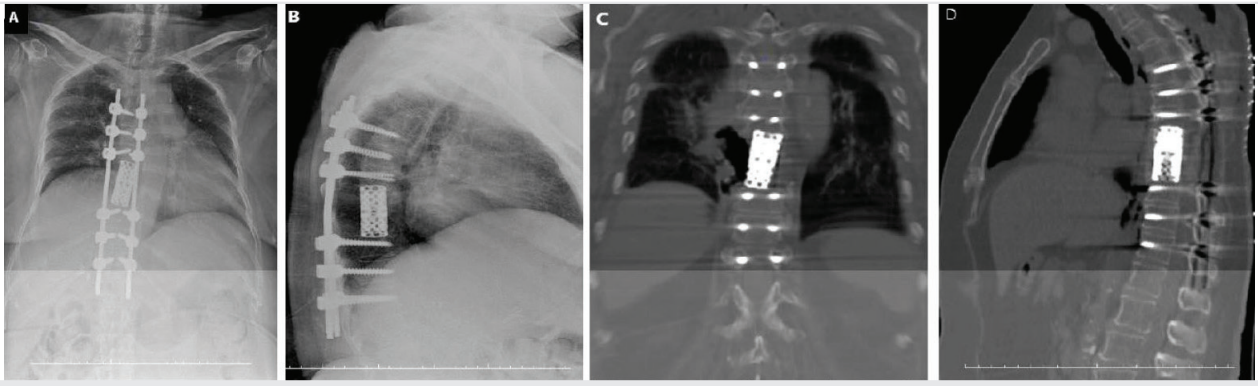


**Figure 2.** (a, b) Post-operative 3rd-month AP-lateral X-ray showing the T4-11 screw rod system (black arrow) and T7-8 corpectomy cage (green arrow). (c, d) Early post-operative coronal and sagittal MPR-CT showing proper positioning of the T4-11 screw rod system (white arrow) and the T7-8 corpectomy cage (blue arrow)
MPR-CT: Multi-planar recon-computed tomography

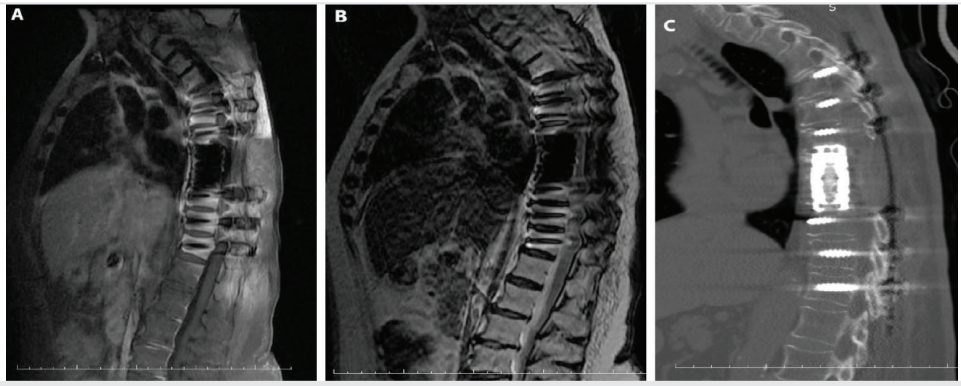


**Figure 3.** (a) Post-operative 1st-year T1W contrast-enhanced sagittal magnetic resonance imaging (MRI) showed no signs of infection in the disc, vertebral corpuscles, or epidural distance. (b) Unenhanced T1W sagittal MRI showing no evidence of infection. (c) Post-operative 1st-year sagittal multi-planar recon-computed tomography showed no signs of infection

## Discussion

While spondylodiscitis is quite common in the general patient population, it usually occurs after osteomyelitis or spine surgery. Discitis occurs in 2% to 7% of osteomyelitis cases (4).

The incidence of spinal infections is gradually increasing because of the increase in the elderly population, immunosuppressive diseases, widespread use of chemotherapy, DM, chronic kidney failure, alcohol consumption, chronic steroid use, and the increase in the number of surgeries worldwide. Among our patients, 3 had DM type 2 and 2 had CRF.

A large literature review on spinal TB reported that most cases occur in Southeast Asia and Africa (2). In the reviewed publications, anti-TB drugs and conservative treatment were the standard treatments. With the exception of spinal instability and neural compression, the role of surgery remains controversial, and definite surgical indications have not been determined (2). The Medical Research Council institution did not offer surgical indications other than abscess, sinus formation due to abscess, and neurological deficit and did not indicate spinal deformities (5,6). However, in many other randomized controlled studies, surgical treatment was the primary choice in the presence of STB, neurological deficit, deformity, and instability, irrespective of the anatomical region (2).

The most feared complication of STB is a neurological deficit, followed by infection-related deformity (7). In conservative treatments, vertebral collapse and kyphosis can be observed up to 15 degrees. Severe deformity is observed in 3%-5% of all cases. Neurological deficit is observed in 10%-40% of cases. Neurological deficits were detected in six (40%) of our patients.

The direction of the surgical approach varies according to the region of spinal involvement. Recent studies recommend anterior approaches that allow stabilization and decompression in the cervical and cervicothoracic spine and rigid posterior interventions that correct deformity in the lower thoracic region and facilitate neural decompression (2,8-10).

Open anterior approaches can significantly limit rehabilitation because of thoracic spine, post-operative pain, and complications. Thoracoscopic interventions were introduced after the 1990s and have been shown to reduce morbidity (11-14). However, these thoracoscopic techniques require special training and experience. The disadvantages of endoscopic interventions include two-dimensional images, disorientation in anatomy, loss of depth sensing, and the requirement of extra investment in thoracoscopic equipment and instruments) (15).

In their series of 10 cases undergoing thoracoscopic interventions, Huang et al. (16) reported a mean blood loss of 485 mL (150-850 mL) and a mean surgical time as 174 minutes (120-240 minutes). Their study

reported a mean kyphotic correction rate of 37.3%. In their series of 23 cases, Jayaswal et al. (17) reported a mean blood loss of 780 mL (330-1180 mL), a mean surgery time as 228 minutes (102-324 minutes) and documented neurological recovery in 94.4% of the cases. Huang et al. (18) reported a mean blood loss of 550 mL (range: 300-1000 mL) the surgery time of 210 min (range: 170-300 min), and showed that back pain was reduced by 92%, and the neurological deficit was reduced by one level in all patients. In our study group, the mean blood loss of patients was 630 mL (range: 350-1100 mL), the mean surgical time was 220 min (range: 170-250 min), pre-operative VAS was 7.7% (7-9), and post-operative VAS was 2.8% (2-3), resulting in a 100% reduction in VAS, and neurological improvement was observed in 88.8% of patients who were not Frankel scale A.

Although minimal or open surgical methods are used for anterior thoracic interventions, it should be noted that the incidence of intervention-specific complications is 24.4-31.3% in the literature (17-21). Apart from general neurological and spinal bone complications, these intervention-specific complications include lung rupture, pulmonary parenchymal damage, atelectasis, respiratory dysfunction, pneumonia, and empyema. In our study, one patient died of to multiorgan failure, whereas others of no complications other than a simple wound infection, which was corrected with medical treatment.

### Study Limitations

This retrospective study had some limitations. First, there was no control group with complete spinal infection surgery. Second, the number of patients was too small to cover the entire population.

Dynamic imaging could not be performed before surgery because of pain or neurological deficits. Therefore, pre-operative kyphosis evaluations were made via CT, and then surgery was planned.

Previous studies on Pott's abscesses in the thoracolumbar region have been conducted using the anterior and anterior- posterior combined approaches. There are few studies on the posterior approach. More studies must be conducted on this subject, and contributions should be ensured to the literature.

## Conclusion

Approaches to ST may include anterior, posterior, and combined approaches. The anterior approach is a very successful method for stabilizing the anterior column and decompressing the spinal cord. However, anterior approaches have high mortality and morbidity rates. Posterior approaches in spine surgery are used more frequently today because of the increasing experience of spine surgeons. This surgical approach maximizes retention and reconstruction of the spine. Therefore, posterior corpectomy and posterior instrumentation may be a safe, effective, and less invasive technique in such patients. In our study, we observed that we successfully treated ST patients using the posterior approach.

**Ethics Committee Approval:** The study was approved by the Sakarya University Local Ethical Committee (approval number: E-71522473-050.01.04-92657-570, date: 03.01.2022).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Surgical and Medical Practices - M.K., D.C.; Concept - M.K.; Design - M.K., D.C.; Data Collection or Processing - M.K.; Analysis or Interpretation - M.K.; Literature Search - M.K., D.C.; Writing - M.K., D.C.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 49-55
**DOI:** 10.4274/imj.galenos.2024.15931

# Safety Evaluation and Tolerability Overview of Favipiravir in the Management of COVID-19: A Real-Life Experience from Turkey

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## ABSTRACT

**Introduction:** Coronavirus diseases-2019 (COVID-19) have been ongoing for more than two years. Despite the scientific research conducted in this process, there is still no widely accepted definitive treatment for the disease. For treating COVID-19, using antiviral agents previously used for the treatment of other RNA-virus infections has been seen as a fast way to a solution, and favipiravir is one of the leading agents. This prospective, multicenter, observational study was designed to investigate the safety of favipiravir in 500 patients treated with favipravir for favipravir.

**Methods:** This study was conducted as a multicenter prospective study. Eight different sites from four cities participated, and 500 patients were included in the study. Follow-up of laboratory parameters, adverse events (AEs), and amelioration of fever, dyspnea, and cough symptoms of the patients was recorded in a case report form.

**Results:** A total of 475 patients from eight centers completed the study. A total of 401 AEs were reported in 206 (51.4%) patients, which were mild-to-moderate in the majority of cases. Serious AEs occurred in 5 patients and death occurred in 4 patients. From the first to the last measurement, serum alanine aminotransferase levels (31.9±27.7 vs. 47.2±49.7 U/L, $p<0.001$) increased, whereas C-reactive protein (39.9±66.4 vs. 15.2±30.5 mg/L, $p<0.001$) and creatine kinase (101.7±187.7 vs. 71.9±43.5 U/L, $p=0.018$) levels decreased. In follow-up parameters, oxygen saturation ($SpO_2$; 96.2±2.7 vs. 97.5±2.1%, $p<0.001$) and amelioration of fever (>37.8 for 6.6% on day 3, 3.2% on day 5, and 0.6% on day 10), dyspnea (for 56.4% on day 5, 62.4% on day 7, and 81.2% on day 10), and cough (46.0% on day 5, 73.0% on day 7, and 87.3% on day 10) were noted in an increasingly higher percentage of patients with continued therapy.

**Conclusion:** The current study provides real-life data of favipiravir, which is a unique option in Turkey for treating COVID-19 patients. The results revealed that favipiravir is a well-tolerated agent with a low side-effect profile. However, it needs to be evaluated with well-designed, dose-compared, randomized controlled studies for the evaluation of efficacy.

**Keywords:** COVID-19, favipiravir, adverse event, safety, real-life, Turkey

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**Cite this article as:** Mete AÖ, Vahapoğlu A, Okatar Erözcan T, Koçak K, Sarıgül F, Zeka AN, Dora DD, Güldaval F, Özütürk B, Anar C, Petek O, Adıgüzel Z, Avkan-Oğuz V, Yalçın AN, Polat G, Turan MO, Demir Ö, Karaoğlan İ, Seyman D, Tunçok Y, Kılınç O, Gökmen AN, İnan D, Türkmen ÜA, Sertoğullarından B, Köse Ş, Erenmemişoğlu A. Safety Evaluation and Tolerability Overview of Favipiravir in the Management of COVID-19: A Real-Life Experience from Turkey. İstanbul Med J 2024; 25(1): 49-55.

**Received:** 15.11.2023
**Accepted:** 05.02.2024

## Introduction

The coronavirus disease-2019 (COVID-19), an infectious disease caused by a novel severe coronavirus designated as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has spread rapidly worldwide and has placed an enormous burden on the healthcare system since its onset in Wuhan, China, at the end of 2019 (1-6).

Although there is currently no worldwide accepted specific antiviral therapy with proven efficacy for COVID-19, the use of potent antiviral agents approved for other viral infections as repurposed drugs against SARS-CoV-2 is considered one of the quickest strategies for the response to the COVID-19 outbreak and a pragmatic way to accelerate the drug approval process (6-9).

Favipiravir is an oral broad-spectrum RNA-dependent RNA polymerase (RdRp) inhibitor that acts as a nucleotide analog that selectively inhibits viral RNA-dependent RNA polymerase or causes lethal mutagenesis after incorporation into viral RNA (5,6,10-12). It is considered to be effective against infections caused by not only influenza virus but also by a wide range of RNA viruses (5,8). Given that SARS-CoV-2 has a genome sequence that is 75-80% identical to that of SARS-CoV, the existing treatment for SARS and middle east respiratory syndrome is suggested to be helpful for developing COVID-19 therapeutics (13,14). Early clinical studies in favipiravir-treated COVID-19 patients have shown promising results in terms of rapid viral clearance as well as improvement in clinical and radiological outcomes compared with other repurposed antiviral drugs (7,8). In the treatment guidelines of many countries, favipiravir has been used for a period of time for the treatment of both outpatients and inpatients, but it has never been used in many other countries (15). However, in some studies published later, the effectiveness was found to be insufficient. It has been used from March 2020 to February 2022 in Turkey, and this study examines the side effects and safety profile in patients who started favipiravir from the first period of use (7,8,15-18). This prospective, multicenter, observational study was designed to investigate the safety of favipiravir in 500 patients under treatment of COVID-19 with favipravir.

## Methods

### Study Population

The study was conducted between 24 December 2020 and 19 February 2021. A total of 500 patients diagnosed with COVID-19 who were prescribed favipiravir (2x800 mg; 1 day, then 2x600 mg; 4 days) treatment were included in this prospective observational study conducted at eight centers across Turkey: XX[1], XX[2], XX[3], XX[4], XX[5], XX[6], XX[7], XX[8] (Table 1). Adult (≥18 years of age) patients with lung computed tomography imaging or reverse transcription polymerase chain reaction analysis-based diagnosis of COVID-19 who were planned to receive favipiravir treatment but not yet received the first dose were included in this study. Patients who had become unable to take oral medication due to disease progression, patients on another trial, and patients with allergy or hypersensitivity to any of the treatment agents and/or any of the excipients of the products as well as those with severe liver disease [Child-Pugh score ≥C, aspartate aminotransferase (AST) >15 times the upper normal limit], severe renal impairment (glomerular filtration rate ≤30 mL/min/1.73 $m^2$) or need for dialysis or renal replacement therapy, and pregnant or breastfeeding patients were excluded from the study. Ethical approval was taken from Gaziantep University Clinical Research Ethics Committee (approval number: 2020/18, date: 24.07.2020). Written informed consent was obtained.

### Study Design

All patients diagnosed with COVID-19 were treated in accordance with the official COVID-19 Adult Treatment Algorithm guidance established by the Republic of Turkey MoH (18). Favipiravir treatment (1600 mg of loading dose BID on day 1 followed by 600 mg BID from day 2 to day 5-rarely up to day 10) was applied in accordance with the prescribing recommendations according to the treatment algorithm established against COVID-19. In line with the observational study design, the decision to initiate treatment with favipiravir, the time of hospital discharge, and the frequency and timing of visits were at the treating physician's discretion (Figure 1). The time frame of this study was defined as 14 days, and at the end of favipiravir treatment, all patients (outpatients, discharged and hospitalized) were followed up for up to fourteen days from the first medication day of the treatment. Outpatients were asked to bring their patient's diary on the day of the end of the study visit. Site investigators examined the patients, and biochemical and hematological analyses were performed if deemed necessary.

### Assessments

In the clinical study, data on patient demographics (age, gender), complete physical examination, vital signs, body temperature (ºC),

**Table 1. Sites and numbers of patients included in the study**

| Patients / Site | Screened | Included | Completed the study | Discontinued |
|---|---|---|---|---|
| Gaziantep University Hospital | 207 | 200 | 198 | 2 |
| Antalya Training and Research Hospital | 131 | 131 | 123 | 8 |
| Dokuz Eylül University Hospital | 55 | 55 | 54 | 1 |
| Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital | 35 | 29 | 25 | 4 |
| Akdeniz University Hospital | 33 | 33 | 27 | 6 |
| Gaziosmanpaşa Training and Research Hospital | 24 | 24 | 23 | 1 |
| İzmir Katip Çelebi Training and Research Hospital | 22 | 22 | 22 | 0 |
| İzmir Tepecik Training and Research Hospital | 6 | 6 | 3 | 3 |

| Study | Medication Days | | End of Study | Early withdrawal |
|---|---|---|---|---|
| | Day 1- Screening and Medication Day | Other Medication Days after Day 1 | Discharge day** or 14th day of the initiation of the medication | |
| Informed consent | • | | | |
| Inclusion/ exclusion criteria | • | | | |
| Demography (Birth date, ethnic group, gender) | • | | | |
| Medical/Surgical history | • | | | |
| Comorbid Condition | • | | | |
| 12-lead ECG | • | | • | |
| Clinical/Physical examination* | • | •* | • | |
| Confusion or Tachicardia* | • | | • | |
| Tachipnoea*,γ | • | | • | |
| $SPO_2$ | • | | • | |
| Difficulty of Breath | | • γ | | |
| Severity of Cough | | • γ | | |
| Biochemistry and haematology* | • | • * | • | |
| Blood pressure, pulse rate*,γ | • | • *,γ | • | |
| Body temperatureγ | • | • γ | • | |
| Chest imaging (CT) or Posteroanterior Lung Graphy | • | | | |
| Enrolment | • | | | |
| Drug administration | • | • γ | | |
| Recovery | | • | • | |
| Phone visit (teleconsultation)β | | • | | • |
| Adverse event questioningγ | • | • γ | • | • |

* For the inpatients, if deemed necessary by the investigator during medication

** If the patient is discharged earlier than 14th day of the study.

γ Patients will be asked to record data into their diaries.

β For the outpatients, if deemed necessary

**Figure 1.** Flowchart of the study

severity of dyspnea and cough, oxygen saturation ($SpO_2$,%), and laboratory findings for hematological and biochemical parameters including platelet counts (x$10^9$/L), D-dimer (µg/mL), prothrombin time [(PT), sec.] and activated partial thromboplastin time [(aPTT), sec.], activated clotting time (sec), alanine aminotransferase [(ALT), IU/L], AST (IU/L), C-reactive protein (CRP, mg/L), creatinine (mg/dL) and creatine kinase [(CK), IU/L] were recorded for the assessment of safety and efficacy of favipiravir. Adverse events (AEs) and serious adverse events (SAEs); symptoms that reduce quality of life and life-threating events were recorded at each visit to assess the safety and tolerability of favipiravir treatment.

During follow-up, improvement in high fever (return of fever within normal limits), dyspnea, and cough severity was evaluated based on the 10-day treatment, while laboratory parameters were compared between the first measurement (examination; on day 1) and the last measurement (final examination; for outpatients: end of their quarantine, for hospitalized patients: day 14 or on the day of hospital discharge in those discharged from hospital sooner than 14 days).

**Mild cough:** Cough that does not affect the quality of life.

**Moderate cough:** Cough affecting quality of life.

**Severe cough:** Cough causing dyspnea.

**Mild dyspnea:** Difficulty breathing but no change in partial oxygen saturation.

**Moderate dyspnea:** Difficulty in breathing, change in partial oxygen saturation, but no need for oxygen support.

**Severe dyspnea:** Difficulty in breathing with need for oxygen support.

### Study Endpoints

The time frame of this study was defined as 14 days. The primary endpoints were safety and tolerability of favipiravir treatment within a time frame of up to 14 days. Safety was evaluated mainly on the basis of the frequency of AEs and SAEs as well as on the abnormal laboratory values (lymphopenia, thrombocytopenia, alterations in ALT, AST, CRP and D-dimer levels and in PT and aPTT from baseline). The secondary endpoint was to follow-up patients based on time to achieve amelioration in fever, dyspnea, and cough as well as time to recovery (discharge or symptoms recovery time) in COVID-19 patients for up to 14 days. Considering tolerance, the administration of the study medication was performed by the investigator(s) and nurse(s) and supervised by a second medical professional to ensure the correctness of drug administration. The administration of the study medication was documented in the Case Report Form (CRF) and/or the patient's diary. Outpatients were responsible for administering their own medication. They were responsible for recording their medications and clinical condition in the diary designed for this study. The diaries were collected and attached to their CRFs after completion of the study.

### Statistical Analysis

The primary analysis was based on a per-protocol dataset that included all study patients who were treated with favipiravir. The chi-square ($\chi^2$) test and Fisher's exact test were used for the comparison of categorical data, while the two-sample dependent t-test and Mann-Whitney U test were used for the analysis of the parametric variables. Data are expressed as mean ± standard deviation (SD), median (minimum-maximum), and percentage (%) where appropriate. $P<0.05$ was considered statistically significant.

## Results

### Baseline Characteristics

Overall, 25 enrolled patients were dropped out during the study because of arousal of conditions consistent with exclusion criteria in patients, withdrawal of consent, or discontinuation of treatment medication. The study population subjected to final analysis comprised a total of 475 favipiravir-treated COVID-19 patients. The mean patient age was 49.5 years (SD: 18.0, range: 18 to 97 years), while the study population was composed of 243 (51.2%) males and 232 (48.8%) females.

### Safety and Tolerance Data

Based on the laboratory findings, from the first (day 1) to the last measurement, a significant increase was noted in platelet count (231.6±76.9 vs. 306.9±100.8 x$10^9$/L, $p<0.001$), serum ALT levels (31.9±27.7 vs. 47.2±49.7 U/L, $p<0.001$).

Due to the clinical records of the study patients, 401 AEs were reported in 206 (51.4%) patients. The majority of the recorded AEs were submitted as "mild" (270; 67.3%) or "moderate" (128; 31.9%) cases (Table 2). Three of the most commonly reported cases were as follows: muscle pain (63; 15.7%), headache (39; 9.7%), and weakness (33; 8.2%) (Table 3). According to the AE form of the patients, clinicians considered

the relation of the event and the study medication to be "certain" for 9 (2.2%) AEs, "probable/likely" for 8 (2.0%) AEs, and "possible" for 298 (74.3%) AEs (Table 2).

Fifteen SAEs occurred during the study and were reported. None of them were considered to be related to the treatment, but to disease progression. Four deaths occurred during this observational study because of complications of the disease (Table 4).

### Follow-Up Data: Improvement in Fever, Dyspnea, and Cough

The fever (body temperature; >37.8) was reported in 8.9% of patients on day 1, ranged from 6.4% to 3.2% from day 2 to day 5, and then decreased remarkably within the next 5 days of therapy (0.6% on day 10) (Figure 2).

The rates for severe dyspnea were 10.1%, 7.6%, and 6.1% on days 1, 2, and 3, respectively, and then decreased remarkably within the next 7 days of therapy (from 4.2% on day 4 to 1.9% on day 10) (Figure 3).

The rates of severe cough were 6.3%, 9.3%, and 6.9% on days 1, 2, and 3, respectively, and then remarkably decreased within the next 7 days of therapy (from 4.0% on day 4 to 0.8% on day 10) (Figure 4).

Amelioration of fever, dyspnea, and cough symptoms was noted in an increasingly higher percentage of patients who continued therapy (Figure 1-3).

**Table 2. Safety data of the study**

| | |
|---|---|
| **Adverse events (n=401)** | |
| **Patients, n (%)** | 206 (51.4) |
| Number of events | 401 |
| **Relation to study medication, n (%)** | |
| Certain | 9 (2.2) |
| Probable/likely | 8 (2.0) |
| Possible | 298 (74.3) |
| Unlikely | 86 (21.4) |
| Total | 401 (100.0) |
| **Severity, n (%)** | |
| Mild | 270 (67.3) |
| Moderate | 128 (31.9) |
| Severe | 3 (0.7) |
| Total | 401 (100.0) |
| **Serious adverse events (n=15)** | |
| Patients, n (%) | 15 (3.7) |
| Number of events | 15 |
| **Relation to study medication, n (%)** | |
| Unlikely | 15 (100.0) |

"Certain" defines an event that occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. "Probable/likely" defines a condition in which the effect of a drug cannot be attributed to the disease present in the same period of time or to the drugs given along with it."Possible" defines a condition in which the effect of a drug can be explained by the disease present in the same period of time or by the drugs given concomitantly. "Unlikely" defines a situation in which the situation occurring at the time a drug is administered cannot be explained by this drug, but may occur with the disease in the same period or with the drugs given together

**Table 3. Details of the adverse events**

| **Adverse events** | **n (%)** |
|---|---|
| Muscle pain | 63 (15.7) |
| Headache | 39 (9.7) |
| Weakness | 33 (8.2) |
| Cough | 31 (7.7) |
| Dyspnea | 27 (6.7) |
| Diarrhea | 23 (5.7) |
| Loss of smell and taste | 18 (4.5) |
| Vomiting | 18 (4.5) |
| Dizziness | 13 (3.2) |
| Lack of appetite | 13 (3.2) |
| Fatigue | 12 (3.0) |
| Constipation | 8 (2.0) |
| Fever | 8 (2.0) |
| Joint pain | 8 (2.0) |
| High ALT value | 7 (1.7) |
| High AST value | 7 (1.7) |
| Sputum | 6 (1.5) |
| Tachycardia | 6 (1.5) |
| Other | 47 (11,7) |
| Total: | 401 (100) |

Other AEs: Abdominal pain, chills, hyperglycemia, dry mouth, insomnia, stomach, sweating, throat ache, low saturation, chest pain, earache, itching, kidney pain, runny nose, sore throat, thrombocytosis, tremors in the feet, abdominal swelling, acute respiratory failure, allergy, blurred vision, feeling of pressure in the chest, hypertension, loss of balance, loss of smell and taste, low pulse, palpitation, sneeze, stiff neck, throat tickle, WBC count, and lymphocyte decrease. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

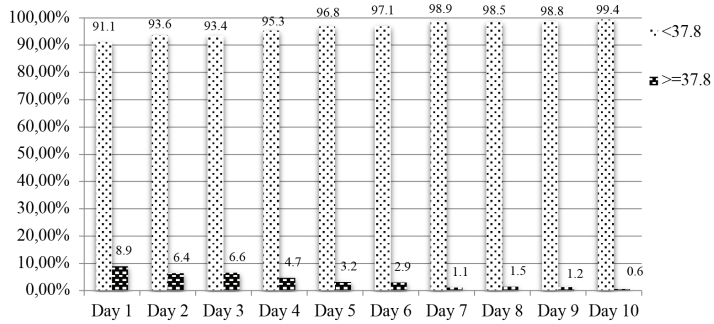


**Figure 2.** Percentage of patients with body temperature of ≥37.8 ºC vs. <37.8 ºC during 10-day favipiravir treatment

**Table 4. Details of the serious adverse events**

| Serious adverse events | Relation to the study medication | Action taken | Outcome |
|---|---|---|---|
| Fever, nausea, and vomiting | Unlikely | Not necessary | Recovery |
| Cardiac arrest | Unlikely | Intensive care | Death |
| Bradycardia | Unlikely | Not necessary | Recovery |
| Need for hospitalization | Unlikely | Not necessary | Not changed |
| Increase in oxygen demand | Unlikely | Not necessary | Full recovery |
| Pneumothorax and low saturation | Unlikely | Not necessary | Death |
| Sepsis | Unlikely | Not necessary | Death |
| Sepsis | Unlikely | Not necessary | Death |
| Respiratory distortion and desaturation | Unlikely | Intensive care | Full recovery |
| High fever, cough, and low saturation | Unlikely | Hospitalization | Full recovery |
| Fever and low saturation | Unlikely | Hospitalization | Recovery but still present |
| Respiratory failure | Unlikely | Intensive care | Full recovery |
| Respiratory failure | Unlikely | Intensive care | Not recovered within the study period |
| Respiratory failure | Unlikely | Intensive care | Recovery but still present |
| Respiratory failure | Unlikely | Intensive care | Not recovered within the study period |

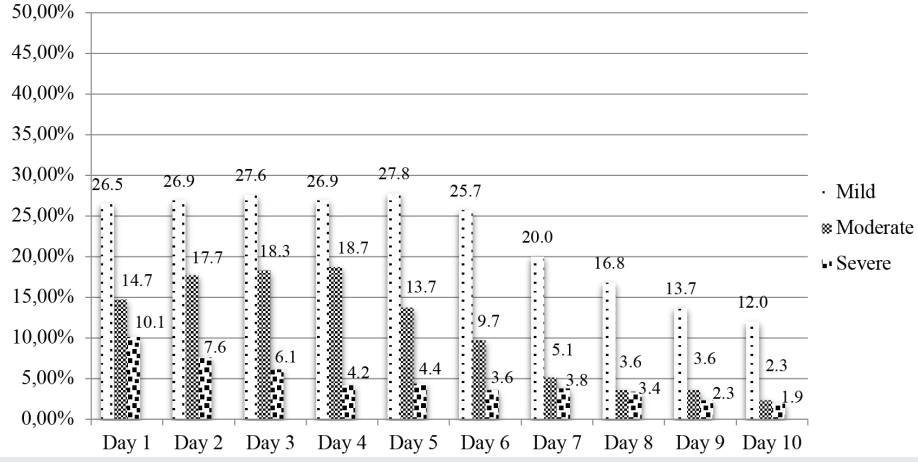


**Figure 3.** Percentage of patients with dyspnea (mild, moderate, severe) during 10-day favipiravir treatment

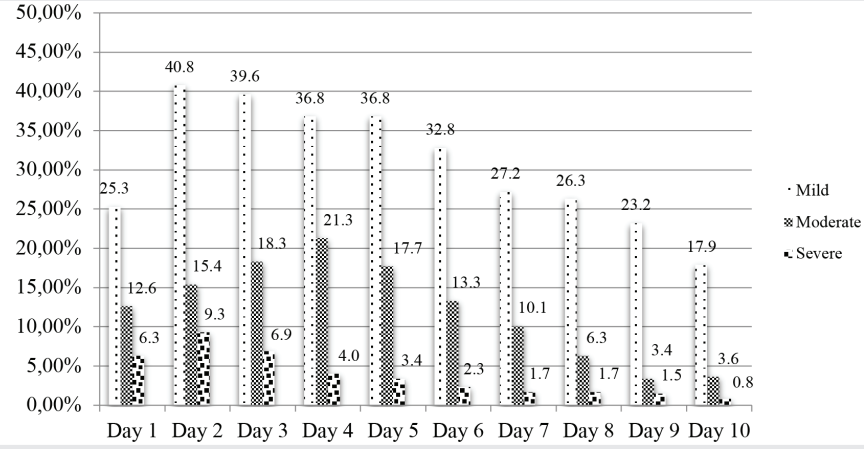


**Figure 4.** Percentage of patients with cough (mild, moderate, severe) during 10-day favipiravir treatment

Nonetheless, the increase in $SpO_2$ levels (96.2±2.7 vs. 97.5±2.1%, p<0.001) and significant decrease in serum levels of CRP (39.9±66.4 vs. 15.2±30.5 mg/L, p<0.001) and CK (101.7±187.7 vs. 71.9±43.5 U/L, p=0.018) were quantitatively determined (Table 3). The average day of discharge from the hospital was 11 days (range; 3 to >14 days).

## Discussion

According to the MoH Guide for the Management of Adults with COVID-19, favipiravir has been accepted as a standard of care in the management of COVID-19 in Turkey for a significant period of time, almost from the beginning of the epidemic. It was almost the only drug in our country at the time of this study. However, it was removed from the standard treatment recommendations in the final guideline.

Here we present the data of the largest prospective real-life observational study of favipiravir-treated COVID-19 patients in Turkey. Our findings revealed a favorable safety profile for favipiravir.

Side effects of oral favipiravir have been detected in both animal and human studies, particularly in repeated dose use. Effects on hematopoietic tissues, changes in liver function parameters, and vacuolization in hepatocytes are frequently observed adverse effects (19).

In addition, testicular toxicity is a reported side effect (20). Favipiravir has teratogenic effects. Therefore, it should be avoided in pregnant women and those with suspected pregnancy (21).

In a meta-analysis of COVID-19 patients treated with favipiravir, the results are similar to those of our study. Although the frequency of side effects is high, they are generally asymptomatic or mild, and the most common side effect is hyperuricemia. There are no serious side effects that require discontinuation of treatment (22,23).

(In other studies) favipiravir has a well-characterized and a favorable safety profile with respect to total and SAEs including 1.1% rate of treatment discontinuation due to AEs and 0.4% rate of SAEs, and a similar proportion of AEs between low and high doses (7,24). Gastrointestinal symptoms, uric acid elevation, decrease in neutrophil count, increase in liver transaminases, psychiatric symptom reactions, and increase in blood triglycerides were considered to be the most common AEs in favipiravir-treated patients (5,7,24).

Notably, the side-effect profile of the drug also seems acceptable in COVID-19 patients, with asymptomatic hyperuricemia and mild, reversible elevation in transaminases being the most frequently reported adverse effects (18).

In the largest database of favipiravir-treated COVID-19 patients from Japan, the authors noted that a total of 3,324 AEs were reported in association with favipiravir use in 2,841 of 10,986 patients. Including hyperuricemia in 1,960 patients (17.8%), liver disorder or elevated liver enzymes in 834 patients (7.6%), and skin eruption or toxicoderma in 129 patients (1.2%) (23).

In the current study, the majority of reported AEs were mild to moderate, with muscle pain headache and weakness as the most common AEs, and none of the SAEs were related to favipiravir. However, observed AEs might be symptoms related to COVID-19 itself. Platelet counts and ALT levels on the last day of treatment were significantly higher than baseline levels, confirming the overall safety and tolerability profile of favipiravir reported in the literature.

### Study Limitations

At the time of the study, there was no approved drug other than favipiravir in our country for this ethical reason; therefore, our study did not include a control group. The efficacy of favipiravir could not be evaluated. In addition, if there is a control group, the relationship of AEs with the drug can be more clearly demonstrated.

## Conclusion

Our findings in favipiravir-treated hospitalized COVID-19 patients revealed the association of favipiravir with improved clinical and laboratory parameters, including timely amelioration of fever, dyspnea, and cough, as well as decrease in serum levels of inflammatory markers without causing safety concerns. Accordingly, the current study provides real-world data of a large patient population in Turkey on the utility of favipiravir while it was the unique option for treating COVID-19 patients. Favipiravir, which was repurposed to treat COVID-19 patients, was revealed as a well-tolerated agent with a favorable safety profile in the management of patients diagnosed with COVID-19. Large-scale randomized clinical trials addressing the efficacy and safety of favipiravir for COVID-19 are needed to further elucidate the role of favipiravir clinical benefits in the management of the ongoing coronavirus pandemic.

**Acknowledgments:** Peri Aytaç, a pharmacist is working as a phase projects manager at Navagenix and supported this study by cordinating study. Onursal Sağlam is General Manager at Novagenix, Emel Doğan Kurtoglu and Merve Gülşah Ulusoy, Biostatistics Specialist at Novagenix Bio Analytical R&D Center In this article, their knowledge on biostatistical information was consulted.

**Ethics Committee Approval:** Ethical approval was taken from Gaziantep University Clinical Research Ethics Committee (approval number: 2020/18, date: 24.07.2020).

**Informed Consent:** Written informed consent was obtained.

**Authorship Contributions:** Concept - F.S., V.A.O., G.P., A.N.G., M.O.T., A.N.Z., B.Ö., C.A., Z.A., A.N.Y., Y.T., A.E.; Design - A.Ö.M., T.O.E., V.A.O., G.P., A.N.Z., B.Ö., Y.T., C.A., Z.A., A.N.Y., M.O.T., F.S., A.N.G., A.E.; Data Collection or Processing - A.Ö.M., A.V., T.O.E., K.K., D.D.D., O.P., F.S., F.G., B.Ö., C.A., Z.A., Ü.A.T., G.P., Ö.D., İ.K., Y.T., O.K., D.S., A.N.G., D.İ., B.S., Ş.K.; Analysis or Interpretation - A.V., K.K., D.D.D., O.P., A.N.Z., F.G., V.A.O., Ö.D., D.İ., B.S., O.K., Ş.K., İ.K., D.S., Ü.A.T.; Literature Search - A.Ö.M., K.K., D.D.D., A.N.Y., M.O.T., İ.K., Ö.D., D.S., O.K., F.G., O.P., D.İ., Ü.A.T., B.S., Ş.K., A.E.; Writing - A.Ö.M., A.V., T.O.E.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 56-62
**DOI:** 10.4274/imj.galenos.2024.61430

# Evaluation of Perioperative Scores Specific to Orthopedic Surgery Related to Intensive Care Admission and Mortality: CCI, ARISCAT and SAPS3 as Valuable Perioperative Orthopedic Risk Scores

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## ABSTRACT

**Introduction:** Estimating intensive care admission of orthopedic patients is challenging because of patient variance and multiple comorbidities, primarily in geriatrics, and not yet standardized for the planned and qualified utility of hospital services. This study aimed to reveal the perioperative risk scores of orthopedic patients followed postoperatively in intensive care to investigate the efficacy of these scores in predicting intensive care admission and mortality.

**Methods:** Patients transferred from the orthopedic ward to the intensive care unit (ICU) at any time during their postoperative follow-up from 2022 to 2023 were investigated. Primarily searched scores were the Surgical Apgar, Wells for pulmonary embolism, Charlson Comorbidity Index, ARISCAT for Postoperative Pulmonary Complications preoperatively, and Simplified Acute Physiology III, Sequential Organ Failure Assessment (SOFA), quick-SOFA, and Acute Physiology and Chronic Health Evaluation postoperatively. These scores were evaluated in relation to total intensive care and hospital stay with mortality.

**Results:** The majority of the study population was found to be ASA-2 (45%). Ninety-eight percent of the patients were admitted to the ICU within three postoperative days, with the indication of planned postoperative follow-up mainly after proximal femoral nailing (24%). Among preoperative scores, wells had a significant positive correlation with ICU readmission and length of ICU stay (r=0.32, p=0.001). 62.7% of the patients had severe Charlson Comorbidity Risk Index. Up to postoperative scores, SAPS3 had a significant positive correlation with total ICU and hospital stay, with a significant difference in mortality (p=<0.001).

**Conclusion:** Among preoperative risk scores, the Charlson comorbidity index and ARISCAT scores could be valuable in predicting the need for postoperative intensive care for orthopedic surgery. Evaluating the daily postoperative SAPS3 score of these patients at the orthopedic ward could help organize patient care services and guide early critical care consultation.

**Keywords:** Surgical Apgar Score, Simplified Acute Physiology Score 3, Wells score, Charlson Comorbidity Index, intensive care, orthopedic surgery

## Introduction

The scope of orthopedic surgeries may include musculoskeletal disorders of young people with concomitant syndromes, geriatric patients requiring major surgery, or trauma patients of all ages and comorbidities. Not surprisingly, these patients may need planned or unplanned intensive care unit (ICU) follow-up because of possible comorbidities or postoperative surgical complications (1). Evaluating the ICU needs of these patients will significantly improve qualified patient management, efficient use of hospital resources, and earlier intervention, resulting in improved morbidity and mortality. To predict the postoperative condition of a patient, there are risk scores perioperatively used but not explicitly studied for orthopedic patients.

Preoperative assessment scores allow for foreseeing the postoperative scenario and expectations regarding the mortality and morbidity of each patient. Many scores have been proposed for this mission, even those specialized to specific surgery types (2). However, probably because of the diversity of patient characteristics and the broad scope of surgeries, a specific scoring system designed for orthopedics and traumatology has not been identified (3). In addition, studies have focused on preoperative indicators in hip surgery because of high mortality rates. However, probably because the population of these surgeries was mainly geriatric, the commonly used preoperative scores, such as the Physiological and Operative Severity Score for enumeration of mortality and morbidity, were found to overestimate mortality (4,5). Therefore, this study was

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**Cite this article as:** Çalışkan B, Boyacı N, Gök MA, Beşir Z. Evaluation of Perioperative Scores Specific to Orthopedic Surgery Related to Intensive Care Admission and Mortality: CCI, ARISCAT and SAPS3 as Valuable Perioperative Orthopedic Risk Scores. İstanbul Med J 2024; 25(1): 56-62.

**Received:** 15.12.2023
**Accepted:** 05.02.2024

designed with a focus on all orthopedic patients needing ICU at any time during their surgical care and to search for the most likely perioperative assessment tool by investigating relevant scores that have not been searched in orthopedics. Therefore, we based our selection of data and scores on possible ICU indications, perioperative unwanted effects, and problems mostly specific to orthopedic surgery in clinical practice. Because most geriatric population has many comorbidities, as the literature implies, it is an ongoing challenge in orthopedics. We searched the Charlson Comorbidity Risk Index (CCI) and the ASA (4,6). Because cardiac and pulmonary complications are higher in association with long bone fractures, clinical frailty, and polypharmacy with comorbidities, the Wells score for pulmonary embolism and ARISCAT score for postoperative pulmonary complications were searched (6-8). To add a practical tool to assess intraoperative variables, especially blood loss, the Surgical Apgar Score (SAS) was selected (9). Because we sought a perioperative assessment for the risk of ICU need and mortality, we included postoperative quick Sequential Organ Failure Assessment (SOFA), SOFA, Acute Physiology and Chronic Health Evaluation II (APACHE II), and SAPS3 scores on the day of ICU admission to enlighten a predictive assessment tool to be used daily in the ward (10-12). All of which are to maintain orthopedic-based qualified care to prevent ICU need or lower mortality by early diagnosis and intervention.

## Methods

This retrospective study was approved by University of Health Sciences Turkey, Haseki Training and Research Hospital Institutional Ethics Committee (approval number: 112-2023, date: 07.06.2023), and all research and analysis were conducted according to the Helsinki Declaration because it was an investigation based on medical records within the hospital informative system, exempted from informed consent. Of 1,192 patients who received orthopedic surgery (emergent or elective) at University of Health Sciences Turkey, Haseki Training and Research Hospital Institutional Orthopedics and Traumatology Department between January 2022-June 2023, 109 patients were transferred to the ICU at any time during their hospital stays. The inclusion criteria were ASA 1-4 patients aged over 18, and if they were readmitted, we evaluated the first ICU admission. The exclusion criteria were patients with incomplete data, patients who were admitted to surgery while in intensive care and transferred back to the ICU, those who developed an intensive care-acquired infection after being admitted to the ICU, or those with a complication unrelated to surgery after ICU admission.

We reviewed the medical records to calculate the selected scores and demographic data. To calculate ASA, SAS, CCI, Wells, and ARISCAT, we used preoperative medical anamnesis, preoperative anesthesia evaluation, laboratory analysis performed at most one day preoperatively, and intraoperative anesthesia forms were re-examined as the source of information. Afterward, medical records highlighted in the ICU consultation and laboratory analysis on the day of ICU admission were used to calculate SAPS3, qSOFA, SOFA, and APACHE II scores. Each medical record was evaluated from hospitalization until discharge, including in-hospital mortality.

### Primary Outcome

The primary outcome was to reveal the study scores of the patients perioperatively transmitted to the ICU with the evaluation of their effect on the length of ICU and hospital stay.

### Secondary Outcome

The secondary outcome was to demonstrate the relationship between the study scores and in-hospital mortality among patients perioperatively admitted to the ICU from the orthopedic ward.

### Statistical Analysis

All analyses were performed using SPSS 15.0 for Windows. Descriptive statistics are given as mean, standard deviation, minimum, and maximum for categorical and numerical variables. Ratios in independent groups were compared using the chi-square test. Two independent group comparisons of numerical variables were performed using the Student's t-test when the normal distribution condition was met and with the Mann-Whitney U test when not. Spearman correlation analysis analyzed the relationships between numerical variables because the parametric test condition was not met. The alpha significance level was set as $p<0.05$. A receiver operating characteristic curve was determined for each prognostic score, and the best sensitivity and specificity for mortality were estimated as the cut-off points.

## Results

**Demographic data of the study population:** The mean age of the patients was found to be 70 years, similarly distributed by gender. 12.8% of the population did not have any comorbidities, and if so, hypertension and diabetes mellitus were the leading diseases among them (Table 1). Notably, the distribution of ASA classifications was

**Table 1. Demographic values of the study population**

| | |
|---|---|
| **Age** | **70.1±16.1 (18-95)** |
| **ASA n (%)** | |
| 1 | 12 (11.0) |
| 2 | 49 (45.0) |
| 3 | 44 (40.4) |
| 4 | 4 (3.7) |
| **Gender n (%)** | |
| Male | 53 (48.6) |
| Female | 56 (51.4) |
| BMI* | 26.5±4.8 (18-40) |
| **Comorbidity n (%)** | |
| Hypertension | 60 (55.0) |
| Diabetes mellitus | 49 (45.0) |
| Coronary heart disease | 39 (35.8) |
| Chronic obstructive pulmonary disease | 21 (19.3) |
| Congestive heart failure | 18 (16.5) |
| Chronic kidney disease | 15 (13.8) |
| Arrhythmias | 8 (7.3) |
| Dementia | 9 (8.3) |
| Psychoneurological diseases | 6 (5.5) |
| Cancer | 5 (4.6) |

*Mean ± SD (minimum-maximum), ASA: American Society of Anesthesiolog, BMI: Body mass index

discovered to be mainly ASA-2. Nine postoperative patients who were excluded because they were exitus before ICU at the surgical ward were found to be ASA-4.

**Data related to anesthesia and surgery:** Most patients who had received proximal nailing surgery needed ICU postoperatively (Table 2).

**Data related to ICU and hospital stay with mortality:** Patients were mostly taken into the ICU within 72 h postoperatively with the indication of planned postoperative follow-up because of patient comorbidities or major surgery (Table 3). The average hospital stay lasts 15.9±13.5 days, and the 30-day mortality was 17.4% among these patients, all concluded at their hospital stay.

### Primary Outcomes

**Surgical Apgar Score:** Most patients (71.3%) was found to have moderate (5-7) scores. In addition, only 19 patients admitted to the ICU had low SASs (Table 4). There was no significant correlation between ICU readmission, length of ICU stay,and hospital stay (p=0.09, 0.95, 0.17) (Table 5).

**Wells score for pulmonary embolism and ARISCAT score for postoperative pulmonary complications:** 82.6% of patients had Wells scores of an unlikely pulmonary embolism, and only three patients had an ICU indication because of clinically suspected pulmonary embolism (Table 4). However, higher scores had a significant positive correlation with the length of ICU stay (Table 5). Meanwhile, 46 patients had moderate to high ARISCAT scores without significant correlation with the length of ICU stay (Table 5).

**Charlson Comorbidity Index:** 62.7% of the patients had severe CCI (Table 4). There was no significant correlation between the length of ICU stay and hospital stay.

**Table 2. Data related to anesthesia and surgery**

| | |
|---|---|
| **The type of anesthesia n (%)** | |
| General anesthesia | 51 (46.8) |
| Combined spinal-epidural | 5 (4.6) |
| Spinal | 46 (42.1) |
| Peripheral nerve block | 1 (0.9) |
| Sedo-analgesia | 1 (0.9) |
| Epidural and general | 4 (3.7) |
| **Surgery (n, %)** | |
| Proximal femoral nailing | 29 (26.6) |
| Hip prostheses | 28 (25.7) |
| Vertebra, instrumentation-laminectomy | 11 (10) |
| Amputation | 16 (14.6) |
| Fracture surgery, lower extremity (intramedullary nailing, osteosynthesis) | 12 (11) |
| Others (debridman, external fixation) | 11 (10) |
| Tumor | 2 (1.8) |
| Surgery time* | 178.5±132.6/44-630 (122.5) |
| Preoperative Hb* | 10.7±2.3/6-17 (10.3) |
| Postoperative Hb* | 9.5±2.0/5.5-14.6 (9.3) |
| Preoperative creatinine* | 1.17±0.88/0.33-4.33 (0.94) |
| Postoperative creatinine* | 1.15±1.04/0.16-6.08 (0.89) |
| Preoperative $SpO_2$* | 93.4±4.1/80-100 (94) |
| Vasoactive drug need n (%) | 40 (36.7) |
| Intraoperative blood loss * | 363.9±582/0-2900 (135) mL |
| Preoperative heart rate* | 89.8±18.2/50-133 (86.5) |
| Perioperative lowest systol* | 94.3±20.6/48-140 (95) |

*Mean ± standard deviation/minimum-maximum (median)

**Table 3. Data related to ICU and hospital stay with mortality**

| | |
|---|---|
| **Time of ICU admission (day)** | |
| Preoperative | 5 (4.6) |
| Postoperative 72 h | 99 (90.8) |
| Postoperative more than 3 days | 5 (4.6) |
| **ICU indication n (%)** | |
| PACU | 68 (62.4) |
| Respiratory insufficiency | 29 (26.6) |
| Pulmonary embolism | 3 (2.8) |
| Heamodynamic insufficiency | 24 (22.1) |
| **Proved infection at ICU admission n (%)** | |
| Culture negative | 69 (63.3) |
| Culture positive | 40 (36.7) |
| Total blood transfusion * | 1.6±1.9/0-9 (1) |
| Total ICU stay* | 3.6±4.1/1-20 (2) |
| Total hospital stay* | 15.9±13.5/4-109 (11) |
| Mortality (30 days) n (%) | 19 (17.4) |

*Mean ± SD/minimum-maximum (median)

**Table 4. Preoperative and postoperative scores**

| | |
|---|---|
| **Surgical Apgar Score*** | **6.1±1.6/2-10 (6)** |
| Low (8-10), n (%) | 19 (17.6) |
| Moderate (5-7), n (%) | 77 (71.3) |
| High (0-4), n (%) | 12 (11.1) |
| **Wells score** | 2.3±2.2/0-9 (1.5) |
| Unlikely (<5 point), n (%) | 90 (82.6) |
| Likely (>4 point), n (%) | 19 (17.4) |
| **Charlson Comorbidity Index*** | 5.0±2.6/0-13 (5) |
| Mild (1-2), n (%) | 13 (12.7) |
| Moderate (3-4), n (%) | 25 (24.5) |
| Severe (>5), n (%) | 64 (62.7) |
| **ARISCAT score *** | 42.0±15.4/8-78 (42) |
| Low (<26), n (%) | 19 (17.4) |
| Medium (26-44), n (%) | 44 (40.4) |
| High (>44), n (%) | 46 (42.2) |
| **Quick SOFA*** | 1.0±1.0/0-3 (1) |
| 0-1 no infection | 77 (70.6) |
| 2-3 possible infection | 32 (29.4) |
| **SOFA*** | 4.4±3.2/0-18 (4) |
| **APACHE II*** | 15.4±8.1/0-41 (13) |
| **SAPS3*** | 57.2±13.7/32-98 (56) |

*Mean ± SD/minimum-maximum (median), SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II

**Quick SOFA, SOFA, APACHE, SAPS3:** Most patients in the orthopedic ward were not found to have sepsis due to low q-SOFA scores by negative culture results from the first samples taken at admission to the ICU (Table 3, 4). SOFA, APACHE, and SAPS3 scores at the same time interval had a significant positive correlation with the length of ICU stay, and SAPS3 also had a significant positive correlation with total hospital stay (Table 5).

### Secondary Outcomes

**Preoperative scores:** SAS, Wells, and ARISCAT were found to be unrelated to mortality because lower scores or higher risks were not apparently distributed to the patients who ended up exitus as expected. Severe CCI was correlated with mortality as % 63.2 of the exitus patients (Table 6).

Postoperative scores: SAPS3 had a higher range between exitus and healthy discharge. For SAPS3, the receiver operating characteristic (ROC) curve area was 0.864 (95% CI: 0.78-0.94) with a 61.5 cut-off point (sensitivity: 73%; specificity: 75) (Figure 1). For APACHE II and SOFA, the ROC curve areas were 0.799 (95% CI: 0.67-0.92) with a 15.5 cut-off point (sensitivity: 73%; specificity: 71%) and 0.738 (95% CI: 0.61-0.86) with a cut-off point 4.5 (sensitivity: 63%; specificity: 63) (Figure 1).

**Table 5. Relationship of Scores length of ICU stays and length of hospital stays**

| | ICU stay | | Total hospital stay | |
|---|---|---|---|---|
| | r | p | r | p |
| Surgical Apgar Score | -0.005 | 0.95 | -0.13 | 0.17 |
| Wells score for pulmonary embolism | 0.32 | 0.001 | 0.16 | 0.09 |
| Charlson Comorbidity Index | 0.04 | 0.61 | -0.071 | 0.46 |
| ARISCAT score | 0.11 | 0.23 | 0.01 | 0.91 |
| Quick SOFA at ICU admission | 0.55 | <0.001 | 0.21 | 0.03 |
| SOFA score at ICU admission | 0.45 | <0.001 | 0.18 | 0.05 |
| APACHE score at ICU admission | 0.45 | <0.001 | 0.09 | 0.3 |
| SAPS 3 | 0.48 | <0.001 | 0.21 | 0.03 |

SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II, ICU: Intensive care unit

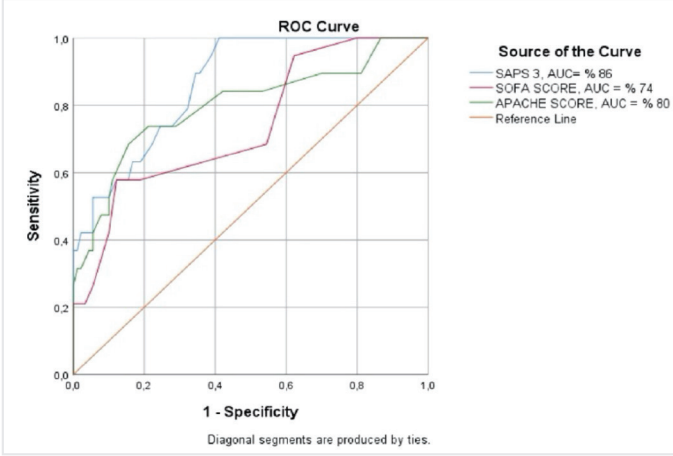


**Figure 1.** SAPS3, APACHE 2, and SOFA scores and mortality
SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II, ROC: Receiver operating characteristic

**Table 6. Scores and mortality (exitus and healthy discharge)**

| | Exitus | Healthy discharge | p |
|---|---|---|---|
| **Surgical Apgar Score*** | 6.6±1.7/3-9 (7) | 6.0±1.5/2-10 (6) | 0.18** |
| Low (8-10), n (%) | 6 (31.6) | 13 (14.6) | 0.19 |
| Moderate (5-7), n (%) | 11 (57.9) | 66 (74.2) | |
| High (0-4), n (%) | 2 (10.5) | 10 (11.2) | |
| **Wells score** | 3.7±2.9/0-9 (3) | 2.0±1.9/0-9 (1.5) | 0.01** |
| Unlikely (<5 point), n (%) | 11 (57.9) | 79 (87.8) | 0.005 |
| Likely (>4 point), n (%) | 8 (42.1) | 11 (12.2) | |
| **Charlson Comorbidity Index*** | 5.0±1.7/2-9 (5) | 5.0±2.8/0-13 (5) | 0.86** |
| Mild (1-2), n (%) | 2 (10,5) | 11 (13.3) | 1.0** |
| Moderate (3-4), n (%) | 5 (26,3) | 20 (24.1) | |
| Severe (>5), n (%) | 12 (63,2) | 52 (62.7) | |
| **ARISCAT score*** | 44.3±12/22-65 (43) | 41.5±16.1/8-78 (42) | 0.47 |
| Low (<26), n (%) | 1 (5.3) | 18 (20) | 0.30** |
| Medium (26-44), n (%) | 9 (47.4) | 35 (38.9) | |
| High (>44), n (%) | 9 (47.4) | 37 (41.1) | |
| **Quick SOFA*** | 1.9±1.0/0-3 (2) | 0,8±0.89/0-3 (1) | <0.001** |
| 0-1 no infection | 8 (42.1) | 69 (76.7) | 0.003** |
| 2-3 possible infection | 11 (57.9) | 21 (23.3) | |
| **SOFA*** | 7.2±4.4/2-18 (7) | 3.8±2.5/0-10 (4) | 0.001** |
| **APACHE II*** | 24.0±10.6/9-41 (21) | 13.6±6.1/0-34 (13) | <0.001** |
| **SAPS3*** | 73.2±13.0/56-98 (75) | 53.9±11.3/32-79 (54) | <0.001 |

*Mean ± standard deviation/minimum-maximum (median), **Mann-Whitney U testi, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II

## Discussion

Our retrospective observational analysis revealed that some perioperative scores were significantly higher in 109 patients perioperatively admitted to the ICU among a total of 1192 orthopedic surgeries and may be useful for generalizing the prediction of the ICU need, length of hospital stays, and mortality in routine clinical practice. Our research suggests that CCI could be a better option for the identification and allocation of ICU resources for orthopedic patients with regard to ASA, Wells, ARISCAT, and SAS scores. Moreover, the higher correlation of SAPS3 compared with SOFA and APACHE scores in the length of ICU and hospital stays seemed promising to navigate the perioperative health care needs of orthopedic patients. In addition, SAPS3 scores, with their higher specificity and distinct cut-off point, may be a more accurate tool for predicting mortality than others for orthopedic patients. Accordingly, among the many preoperative and postoperative prognostic scores that can be used in the care of orthopedic patients, especially for planned proximal femoral nailing and partial prostheses, CCI and SAPS3 scores seem to be more relevant.

Although postoperative critical care has been reported to be required mainly after spine surgeries, in our institution, patients in the ICU had mostly geriatric lower extremity fractures (13). This could be due to the perception of our anesthesiology and reanimation department about the utility of postoperative critical care based chiefly on patient comorbidities. This is the reason for this study to investigate CCI, especially for orthopedic surgery. Under our understanding of ICU needs, patients are primarily admitted postoperatively with the ICU indication (62.4%) as planned post-anesthesia care, and 95% have comorbidities with moderate to severe CCI (87.2%).

Interestingly, however, most of our patients were ASA-2, and only four were ASA-4. Although previous literature implies its reliability related to hospital stay and mortality, these studies were restricted to arthroplasties, and no study reflecting its usefulness in the general orthopedic population has not yet been published (14). Therefore, we assumed that the physical status classification of orthopedic patients could not be as valid as that in other surgical populations because it would be subjective to evaluate a disabled geriatric patient with a physical activity score.

The second most frequent ICU indication for postoperative orthopedic patients was respiratory insufficiency, with only a few being diagnosed with pulmonary emboli. This is not surprising with trauma patients, especially long bone fractures in orthopedics, because of the known complexity of managing a prothrombotic state after trauma and immobility due to extremity injury along with the risk of bleeding due to anticoagulants and surgery (7). Therefore, a risk assessment tool for deep vein thrombosis may guide further preoperative examination and predict the need for postoperative respiratory support in the ICU (15). In our study, as its utility in trauma and orthopedic patients is a valid tool, we evaluated the Wells score, and most postoperative patients admitted to the ICU were found to have a low risk for embolism (7,15,16). However, we also searched for a novel tool recently used for non-thoracic surgery but not for orthopedic surgery (8,17,18). Notably, ARISCAT scores within our study were found to be high, as expected because these patients were admitted to the ICU because of respiratory insufficiency. Thus, the ARISCAT score seems correlateded than Wells scores in postoperative orthopedic patients because of our results and promising further research.

Moreover, other than preoperative evaluation, intraoperative assessment with SAS has been shown to predict postoperative ICU admission because its relationship with postoperative complications and mortality is well-described (9,19). However, its correlation with ICU admission has been revealed in previous studies of abdominal surgeries (9). For orthopedic surgery, research is limited to its relation to increased complications after arthroplasties and spine surgeries (20,21). SAS scores of our patients were relatively moderate, and only 11% of ICU-admitted patients had low scores. The reason was obvious when we observed that the data of mean intraoperative blood loss, heart rate, and lowest systole or even amount of blood transfusion of our patients were not significant, possibly due to tourniquet and tranexamic acid use in orthopedic surgery (Table 2) (22). Consequently, SAS may not be a valid tool for orthopedic surgery to assess ICU admission and mortality.

Association of Critical Illness Scores (APACHE, SOFA) are crucial for critical care because they are accepted as indicators of ICU and total hospital stay, especially mortality (11,12). Furthermore, another mortality estimation score, SAPS3, has demonstrated its utility as a predictor of postoperative ICU admission (10). Therefore, our study searched these scores on the day of ICU admission at the surgical ward to analyze and compare if they could be used as an indicator before ICU admission and revealed that SAPS3 could be the score of choice for orthopedic surgery with its higher sensitivity and specificity than the others and it could help to organize hospital searches with its strong correlation to length of ICU and hospital stay.

### Study Limitations

Our data represent a single-center observation of an orthopedic center of the same type of surgery with the same anesthesiologist deciding the need for critical postoperative care. In a center in which oncologic surgeries are the majority or having a PACU for only 24-h follow-up, ICU indications would be different from ours. Therefore, our study could guide the creation of an orthopedic-based risk assessment score, but it still needs to be investigated in a multi-centered design. Because most geriatric patients with comorbidities need ICU, additional comorbidity measures could be valuable to evaluate. However, we preferred the accustomed CCI, and future research comparing comorbidity- and frailty-based scores, such as age-adjusted CCI or clinical frailty scale, would clarify the most appropriate comorbidity index for orthopedic patients (14).

Although the association between perioperative myocardial injury and cardiovascular outcomes appeared in our study with hemodynamic insufficiency (19.3%) after orthopedic surgery, we could not analyze the troponin levels of each patient because of missing data in our retrospective analysis (23). In addition, it would be wise to add the type of surgery that

was shown to be related to increased mortality or ICU admission to create a risk assessment tool. As we demonstrated in our study, hip fractures and amputations could be compatible with previous literature as they were shown to be related to increased mortality (24,25). In addition, based on our results, most compatible scores, such as CCI and SAPS3, should be accompanied by a cognitive assessment of patients, which were shown to be mostly at older age to complete a specified risk assessment for orthopedic surgery because delirium is a major contributor to mortality, length of hospital stay, and critical care (26).

## Conclusion

Standardized risk stratification designed especially for orthopedic surgery is essential to improve the organization of hospital care services through proper prediction of ICU needs, length of hospital stay, and mortality. A combination of scores proven significant in intensive care admitted postoperative orthopedic patients, as revealed in this study, CCI, ARISCAT, and SAPS3, could be used and provide incipiency for further research.

**Ethics Committee Approval:** This retrospective study was approved by University of Health Sciences Turkey, Haseki Training and Research Hospital Institutional Ethics Committee (approval number: 112-2023, date: 07.06.2023).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Surgical and Medical Practices - B.Ç., N.B., M.A.G., Z.B.; Concept - B.Ç.; Design - B.Ç.; Data Collection or Processing - N.B., M.A.G., Z.B.; Analysis or Interpretation - B.Ç.; Literature Search - B.Ç.; Writing - B.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 63-6
**DOI:** 10.4274/imj.galenos.2024.38485

# Confirmation of Nasogastric Tube Placement via Bedside Ultrasound in a Pediatric Intensive Care Unit

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## ABSTRACT

**Introduction:** Nasogastric tube (NGT) placement is a common procedure in pediatric intensive care and requires accurate verification to avoid complications. Traditional methods such as auscultation and radiography pose limitations such as unreliability and radiation exposure. The aim of this study was to confirm the placement of NGT using bedside ultrasonography (USG).

**Methods:** A prospective study was conducted in a tertiary pediatric intensive care unit (PICU) using bedside USG to confirm NGT positioning. The study included 46 patients, with procedures ranging from November 2023 to January 2024. Placement confirmation techniques included USG visualization and the air bolus method when necessary.

**Results:** All 68 NGT insertions were successfully visualized using USG. The median age of patients was 18 months, with the most common admissions being pneumonia and septic shock. An air bolus was used in 13.2% of the cases to indirectly confirm placement.

**Conclusion:** Bedside USG is an effective and safe alternative for confirming NGT placement in the PICU, minimizing the risk of radiation, and leveraging the benefits of immediate and accurate bedside assessment. This method can replace radiography as the new standard for NGT placement confirmation.

**Keywords:** Nasogastric tube, pediatric intensive care units, radiography, ultrasonography

## Introduction

The nasogastric tube (NGT) has been in use since the 17th-century and was initially used solely for providing nutrition. Currently, NGTs are used for other purposes such as medication administration, stomach decompression, and gastric lavage (1,2). Verifying the placement of the NGT is crucial because accidental insertion into the respiratory tract can carry risks of morbidity and mortality associated with serious complications such as pneumothorax, pneumonia, and death. There have been reports of tube placement errors in children. Here, an error is defined as the placement of the tube in any location other than the desired one (3).

Frequently, auscultation is used to check the placement of a NGT (4). After the NGT is inserted, a stethoscope is placed on the epigastric region of the abdomen, and the placement is confirmed by hearing the pushed air (5). However, this method is not always reliable because similar sounds can be heard even when the tube is misplaced. The appearance and pH value of the aspirate can provide some clues. In the gastric pH test, the pH of the aspirate is checked, and if the pH is below 5.5, the placement of the tube is confirmed (6). However, this may not be definitive in cases where acid-suppressing medication is used. The most reliable method to confirm the position of the NGT, especially in critical or unconscious patients, is considered the "gold standard" and involves abdominal radiography. However, this method also increases radiation exposure (4,7).

Bedside ultrasound has been increasingly used in pediatric intensive care in recent years. In addition to invasive methods such as central venous catheter insertion, evaluation of lung parenchyma, pleural space, abdominal organs, and measurement of cardiac functions can be considered among its usage (8). The use of ultrasonography (USG) for verifying the placement of NGT is increasingly preferred because

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**Cite this article as:** Çolak M, Ceylan G, Topal S, Saraç Sandal Ö, Atakul G, Soydan E, Hepduman P, Kararslan U, Ağın H. Confirmation of Nasogastric Tube Placement via Bedside Ultrasound in a Pediatric Intensive Care Unit. İstanbul Med J 2024; 25(1): 63-6.

**Received:** 26.01.2024
**Accepted:** 05.02.2024

of its numerous advantages. These include widespread availability, ease of application, ability to perform repeated evaluations, bedside assessment, speed, cost-effectiveness, lack of ionizing radiation exposure, high spatial resolution, and dynamic imaging capabilities. However, there are only a limited number of studies in the literature concerning the verification of NGT placement using USG (9).

In this study, our objective was to determine the placement of NGT in patients using USG in the pedaitric intensive care unit (PICU). By employing this imaging technique, we aim to accurately confirm the position of the tube without exposing the patients to radiation, thereby offering a safer and effective alternative for verification.

## Methods

### Study Design

This prospective study was conducted in a 24-bed tertiary-level PICU at University of Health Sciences Turkey, Behçet Uz Pediatric Disease and Surgery Training and Research Hospital. The study period spanned from November 15, 2023 to January 15, 2024, encompassing patients undergoing inpatient treatment. NGTs were inserted by pediatricians following a standard protocol.

### Methodology

Before NGT insertion, the distance from the tip of the patient's nose to the earlobe and from the earlobe to the midpoint between the xiphoid process and the umbilicus (the nose-ear-mid-umbilicus method) was meticulously measured (10). Post-insertion, each patient underwent an ultrasound examination by a certified pediatric intensive care fellow. A Philips HD15 ultrasound machine (Philips, Eindhoven, Netherlands), fitted with a 3-12 MHz linear probe, was employed for the imaging procedure. The positioning of the NGT was initially determined via ultrasound, followed by confirmation through abdominal radiography and/or auscultation. Radiological imaging was exclusively applied in cases where clinical necessity extended beyond the mere confirmation of NGT placement. Such imaging was performed only when clinicians identified additional diagnostic requirements, separate from the verification of NGT positioning.

### Ultrasound Examination

NGT was visualized using longitudinal and angled scans of the epigastrium. In cases where ultrasound examination did not conclusively confirm NGT placement, an air bolus was administered through the NGT using a syringe. The dynamic observation of air movement within the stomach conclusively verified the correct placement of the NGT.

### Ethical Statemnet

The study was approved by the Clinical Research Ethical Committee of University of Health Sciences Turkey, Behçet Uz Pediatric Disease and Surgery Training and Research Hospital (approval number: 2023/16-05, date: 09.11.2023). Informed consent was obtained from the families of patients participating in the study.

### Statistical Analysis

For the data analysis, SPSS 20.0 software was used. The conformity of the data to a normal distribution was assessed using the Shapiro-Wilk test. The ages of the patients and their Pediatric Index of Mortality 3 scores are presented as the median, ranging from the 25$^{th}$ to 75$^{th}$ percentile (Q25-Q75).

## Results

A total of 68 procedures were performed on 46 patients admitted to the PICU. The median age of the patients was 18 months (Q25-Q75: 13-48). Pneumonia was the most common diagnosis requiring intensive care, followed by septic shock (Table 1). Fourteen of all patients underwent tracheostomy. Twenty-two patients were orotracheally intubated and were receiving mechanical ventilator support.

Out of the total procedures performed, in 59 cases, which accounts for 86.7%, the placement of the NGT was directly visualized using USG (Figure 1). In nine of these procedures, visualization required the injection of an air bolus into the NGT. In cases where direct visualization of NGT placement was not initially possible, the air injection technique enabled confirmation. Such scenarios where indirect methods were required accounted for 13.2% of the total procedures performed in our study. This technique was particularly useful in cases where direct visualization of NGT placement was challenging or unclear. The introduction of the air bolus into the NGT enhanced the ability of USG to confirm correct tube placement, thereby enhancing the safety and reliability of the procedure. Thus, the NGT location could be confirmed using bedside USG in each procedure in the study.

## Discussion

This study aimed to validate the positioning of NGT in critically ill pediatric patients using bedside USG. USG is a non-invasive and radiation-free method, in contrast to the traditional gold standard of direct radiographic imaging (8,11). Direct radiography is preferred for definitive confirmation of NGT placement; however, this method

**Table 1. Characteristics of patients undergoing nasogastric tube placement**

| | |
|---|---|
| **Etiology** | |
| Pneumonia | 27 (58.6%) |
| Septic shock | 6 (13%) |
| Metabolic disease | 5 (10.8%) |
| Status epilepticus | 3 (6.5%) |
| Post-cardiac surgery | 2 (4.3%) |
| Chronic lung failure | 2 (4.3%) |
| Tracheomalacia | 1 (2.1%) |
| **Gender** | |
| Male | 27 (58.6%) |
| Female | 19 (41.4%) |
| Age (month)* | 18 (13-48) |
| PIM 3 score* | 1.48 (1.1-2.3) |

*The values have been presented as the median (25$^{th}$ percentile-75$^{th}$ percentile), PIM 3: Pediatric Index of Mortality 3

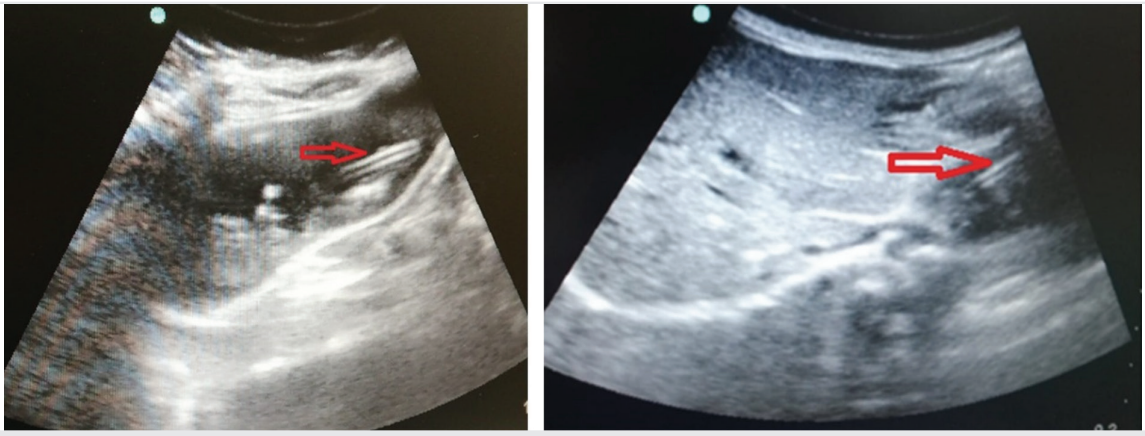

**Figure 1.** Imaging of nasogastric tube placement using ultrasound
*The red arrow points to the nasogastric tube as visualized by ultrasound imaging

involves a risk of repeated radiation exposure, particularly in the pediatric population. USG could be an alternative that eliminates this risk while providing quick and accurate results.

The primary finding of our study was the accurate demonstration of NGT placement in all applications. Thanks to a special USG device used in the intensive care unit, the procedure was performed without loss of time or additional workforce. Since the team placing and imaging the NGT was the same, there was no need for radiologists or radiology technicians, thus saving both labor and time. In a study conducted in pediatric intensive care, all NGTs placed were verified by a radiology expert using bedside USG. Although the results in our study were similar, itis important to note that the verifier using USG was a pediatric intensive care specialist.

In all nine procedures (13.2%), it was necessary to inject air into the NGT to confirm its placement. If the NGT is not directly observable, injecting an air bolus and observing it with USG is an effective method. This air bolus application was particularly useful in cases where air artifacts were observed (12).

In a pediatric intensive care study with 21 patients, all NGTs were visible by ultrasound, achieving 100% sensitivity and without the need for air or saline injection (10). However, in our study, although we could visualize all NGTs, air injection was necessary in 13.2% of cases to confirm placement. This suggests variability in the NGT visualization techniques, even with high success rates. Furthermore, a review of pediatric and neonatal studies reported a sensitivity range of 88% to 98.1% for NGT confirmation, and a meta-analysis in adults showed a sensitivity of 93% and specificity of 97%, indicating effectiveness in confirming correct placements (13,14).

This study supports the adoption of USG as a new standard for detecting NGT placement in children, replacing the gold standard of radiography. This method can avoid unnecessary exposure of patients to X-rays. Additionally, USG imaging, which is low-cost and conducted by the treating physician, saves both labor and time, enhancing efficiency. However, although our study identified all NGT placements, previous studies have shown variable results, indicating that the outcome may not be as definitive as radiography.

**Study Limitations**

Limitations of the study include its single-center nature and the fact that the procedure was performed by intensive care specialists experienced in USG. In addition, the absence of any mispositioned NGT attempts in the study is another limitation. We believe that it is important to demonstrate the sustainability and consistency of this technique through multicenter studies conducted not only by experienced pediatric intensive care specialists but also by pediatricians.

## Conclusion

This study offers an alternative approach to traditional radiographic methods by examining the validation of NGT placement in the pediatric intensive care setting using USG. USG has been found to be effective in determining the correct placement of NGTs without radiation exposure. Future studies conducted by physicians with varying experiences in different centers will be beneficial to demonstrate the feasibility of this method.

**Ethics Committee Approval:** The study was approved by the Clinical Research Ethical Committee of University of Health Sciences Turkey, Behçet Uz Pediatric Disease and Surgery Training and Research Hospital (approval number: 2023/16-05, date: 09.11.2023).

**Informed Consent:** Informed consent was obtained from the families of patients participating in the study.

**Authorship Contributions:** Surgical and Medical Practices - M.Ç., Ö.S.S., G.A.; Concept - M.Ç., G.C., S.T., U.K., H.A.; Design - G.C., E.S., U.K., H.A.; Data Collection or Processing - M.Ç., G.C., S.T., Ö.S.S., E.S., P.H.; Analysis or Interpretation - M.Ç., Ö.S.S., G.A., P.H., U.K.; Literature Search - G.C., S.T., G.A., E.S., P.H.; Writing - M.Ç., H.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 67-71
**DOI:** 10.4274/imj.galenos.2024.88225

# Evaluation of the Anterior Ethmoidal Artery Course in Pediatric Patients

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## ABSTRACT

**Introduction:** The anterior ethmoidal artery (AEA) is an important structure to be considered in endoscopic endonasal surgery, which can lead to serious complications due to injury. We aimed to reveal AEA's course and age-dependent variations and the relationship with closely related structures in pediatric cases.

**Methods:** The paranasal sinus computed tomography of patients under 18 years was retrospectively reviewed. The coronal reformated plane, which is perpendicular to the hard palate, was used for measurements. The AEA was assessed for its course at or below the skull base, and the distance was measured. In addition, the depth of the olfactory fossa (DOF) and nasal septal deviation (NSD) were measured.

**Results:** A total of 156 patients were enrolled in this study. As the DOF increases, the AEA skull base distance also increases ($p<0.005$). In addition, both DOF ($p=0.014$) and AEA skull base distance ($p=0.004$) increase with age. The age of the patients with NSD was higher than that of the patients without deviation ($p=0.035$). Although not statistically significant, a slight increase in both AEA skull base distance and DOF was noted on the NSD side ($p>0.05$).

**Conclusion:** These results show that the olfactory roof anatomy and NSD are not only related to the embryonic period but also an ongoing process after birth.

**Keywords:** Anterior ethmoidal artery, pediatric, skull base, ethmoid roof, nasal septal deviation, olfactor fossa

## Introduction

Revealing the anatomy of the anterior skull base and ethmoid roof has become essential with endoscopic endonasal surgery (1). The endoscopic endonasal approach is increasingly used in current medical practice for skull base, nasal cavity, orbit, or paranasal sinus surgery (2,3). The anterior ethmoidal artery (AEA) is an important landmark for surgeons in endoscopic surgery (4,5). The anatomy of the anterior skull base can be revealed in detail preoperatively using computed tomography (CT) (6). There are three detection points of the AEA on the skull base: the anterior ethmoidal foramen (on the medial orbital wall), the anterior ethmoidal canal (in the anterior ethmoidal sinus or skull base), and the anterior ethmoidal sulcus (on the lateral lamella of the cribriform plate) (4,7-9). Incidental injury of AEA during endoscopic surgery can cause fatal complications such as hematoma or vision loss. The relevant anatomy and location of the AEA need to be revealed individually before surgery to avoid these complications (4,10).

The olfactory fossa is susceptible to injury during endoscopic surgery such as AEA and is closely related to AEA. Different studies have been conducted to reveal and predict the risks of complications in this area during endoscopic surgery (11-13). Keros (12) defined a widely accepted classification of the depth of the olfactory fossa (DOF) to predict complications. They classified the depth of the fossa into three groups: deepest type 3, intermediate 2, and shoaliest type 1 (12).

The nasal septum is another structure related to the ethmoid roof. It runs down from the anterior skull base to the palatine bone. Nasal septal deviation (NSD) may be associated with asymmetries of related areas such as the palatine area and nasal roof (14,15).

Endoscopic endonasal surgeries are in use at increasing rates, especially in the pediatric population, because of their advantages (16,17). The relationships of anatomic structures of the skull base can be more complex because of the nearing locations of landmarks and the continuing process of development and ossification in the pediatric population (18,19). Therefore, surgeons might pay extra attention to revealing the variations of the skull base preoperatively in pediatric cases.

Distinct studies were conducted to reveal the anatomic relationships and variations for predicting and avoiding the complications of endoscopic surgery. However, most of these studies were conducted in

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**Cite this article as:** Aksoy DÖ. Evaluation of the Anterior Ethmoidal Artery Course in Pediatric Patients. İstanbul Med J 2024; 25(1): 67-71.

**Received:** 31.01.2024
**Accepted:** 07.02.2024

adults (2,10,15,20,21). This study reveals the course of AEA and age-dependent variations in pediatric cases. The second aim was to reveal the relationship between AEA and the olfactory fossa and nasal septum, which are structures closely related to AEA.

## Methods

### Data Collection

The University of Health Sciences Turkey, İstanbul Training and Research Hospital Institutional Ethical Review Board approval was obtained for this study (approval number: 59, date: 10.03.2023). We scanned the hospital archive system retrospectively for patients who underwent paranasal CT from January 2020 to January 2023. We enrolled the CT images of pediatric patients (age; ≤18) with slice thickness equal to or less than 1 mm, which is suitable for reconstruction with multiplanar reformat imaging. The exclusion criteria were craniofacial anomaly, trauma with fracture, history of surgery, sinonasal tumor, fibro-osseous mass lesions, or other situations that distort the maxillofacial or skull base area.

### CT Imaging and Radiological Measurements

CT images were acquired with a 64-slice CT scanner (MSCT; Brilliance 64, Philips Medical System, Best, Netherlands). All scans were obtained as routine CT of paranasal sinus imaging in the supine position. The scanning protocol was caudocranial in extent from the hard palate to the end of the frontal sinus, with a field of view of approximately 140-160 mm. The slice thickness was 0.67-1 mm with automatic exposure at 120 kVp and 80-140 mAs. Multiplanar reconstruction was performed with the bone kernel (Widow Wide: 3000-4000 HU, Window Center: 300-500 HU) in three-dimensional (axial, coronal and sagittal) plans. Images were evaluated using the picture archiving and communication system, and coronal plane images perpendicular to the hard palate were used for measurements. All assessments and measurements in this study were performed by the same radiologist (D.Ö.A.). First, the location of the AEA was revealed relative to the anterior ethmoidal foramen. The anterior ethmoidal canal was identified and recorded to determine whether the trace of the canal was in the skull base or under the skull base (4,7,8) (Figure 1A). The distance between the skull base and anterior ethmoidal canal was measured if the trace was under the skull base. The distance between the cribriform plate and the horizontal line passing through the superolateral end of the lateral lamella was measured as the height of the olfactory fossa (22) (Figure 1B). DOF was graded as Keros type 1 (<4 mm), Keros type 2 (4-7 mm), and Keros type 3 (>7 mm) as defined by the Keros classification (12). The cases were evaluated for the presence of NSD. If NSD was present, the side of the angulation was recorded and the deviation angle was calculated. The NSD angle was measured where the angulation of the nasal septum was the most on the coronal plane according to the line extending from the crista galli to the crista nasalis (Figure 1C) (23). All measurements and classifications were performed on either the right or left side.

### Statistical Analysis

The mean, median, minimum, maximum, and standard deviation frequency and percentage were used for descriptive statistics. The distribution of variables was checked using the Kolmogorov-Smirnov test. The Kruskal-Wallis test and Mann-Whitney U test were used for the comparison of quantitative data. The chi-square test was used to compare the qualitative data. Correlation between variables was tested with Spearman's correlation. SPSS 28.0 was used for statistical analyses.

## Results

A total of 156 patients were enrolled in the study after excluding cases that met the exclusion criteria mentioned above. There were 81 female and 75 male patients. The mean age was 7.65±4.07 years. The AEA canal passes through the skull base on 109 of the right side and 111 of the left side. When the right and left sides were included in the evaluation separately, 71% of the 312 sides coursed at the skull base, whereas 29% were freely under the skull base. The mean value of the distance from the skull base was 0.36±0.70 mm (right: 0.38±0.70, left: 0.34±0.69) of the AEA canal in all patients. NSD was not detected in 61 patients. The

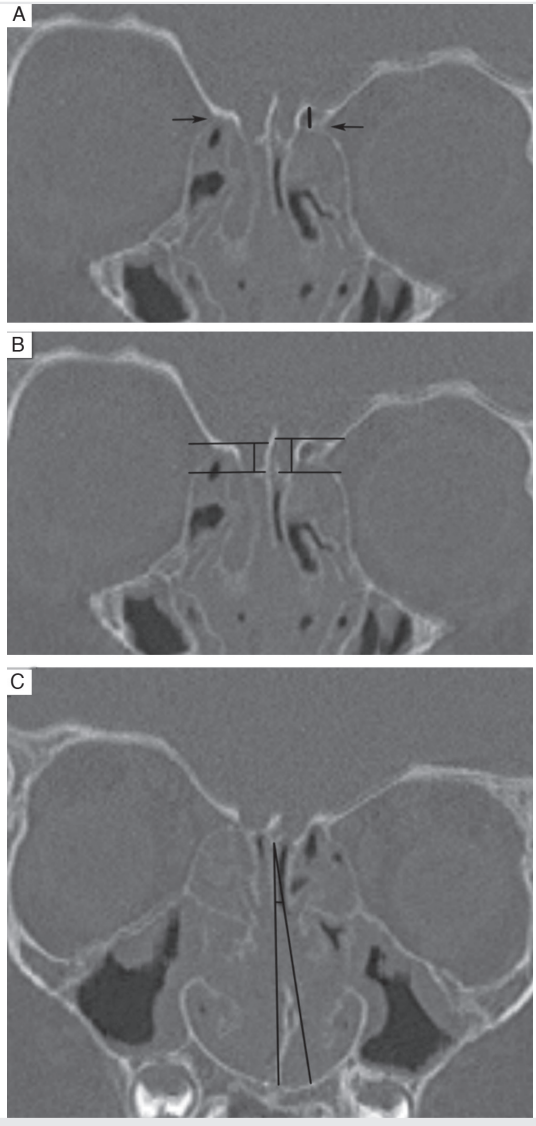


**Figure 1.** Assessment and measurements of the anterior ethmoidal artery (AEA course at the skull base on the right and below the skull base on the left) (A), olfactory fossa depth (B), and nasal septal deviation (C)

deviation side was to the right in 55 patients and left in 40, of a total of 95 patients who had NSD. The mean DOF was 4.23±1.88 on the right and 4.23±1.91 on the left. When we classified the DOF of both sides, we observed 131 (60 right, 71 left) Keros type 1, 163 (86 right, 77 left) Keros type 2, and 18 (10 right, 8 left) Keros type 3.

There was a positive correlation between age, distance of AEA to the skull base, and DOF (Table 1). The mean age of the patients with NSD (8.24±4.11) was higher than that of the patients without NSD (6.74±3.85) (p=0.035) (Table 2). The mean value of the right-sided deviation was 10.34±5.07 degrees and the left-sided deviation were 13.16±4.69. The degree of the left side was higher than that of the right side degree (p=0.02). We did not detect any significant difference between the side of the NSD and the depths of the olfactory fossa or the distance of the AEA from the skull base for both sides (Table 3). The AEA distance was significantly higher in the Keros Type 3 group than in the Keros type 1 and type 2 (p<0.05). In addition, in the Keros type 2 group, it was significantly higher than in Keros type 1 (p<0.05). The mean distances of AEA to the skull base of Keros types are summarized in Table 4.

## Discussion

Preoperative imaging of the ethmoid roof and the identification of anatomical landmarks are crucial for endonasal surgery (24). A variation that might be seen in the anatomy of this area is a situation that may challenge surgery. Awareness of anatomical variations helps prevent vital complications such as bleeding or skull base injury. In particular, in children, the close location of the relevant anatomical structures is another challenging situation and requires more attention (16,25). CT is an appropriate and accepted imaging method for defining the nasal, paranasal, and ethmoid roof areas (10,26).

One of the dangerous parts of the ethmoid roof and one of the landmarks for endoscopic surgery is the AEA (21,26,27). The location of the AEA shows variability individually (26). In particular, the AEA, which runs below the skull base, is more susceptible to injury (7,28). In their study on cadavers (ages not stated), Simmen et al. (26) showed that the AEA was located below the skull base in 35% of the cases. Başak et al. (29) found that 43% of the AEA traces were below the skull base in their study of cases over 15. In another study conducted by Başak et al. (30), including some of the same authors, it was stated that the AEA extends below the skull base in 26% of cases between the ages of 8 and 16. They also compared the results of these two studies and detected a significant difference between young and adults during AEA (p=0.004) (30). Another study stated that the course of AEA at the skull base was more common in cases under 18 years than in those over 18 years (49% vs. 44%; p=0.024) (3). In this study, the AEA trace was found at the skull base in 71% of the pediatric cases. The percentage we obtained is closer to that of studies conducted with pediatric cases in the literature. The mean distance of the AEA from the skull base was different in different studies. The mean value was 1.93 mm (18-86 years, range: 0-7.50 mm) in the study of Abdullah et al. (10), 3.5 mm (cadaver unknown, range 1-8 mm) in the study of Simmen et al. (26), 1.37 mm (18-66 years, range: 0-8.35 mm) in the study of El Anwar et al. (2), and 2.40 (adult, range: 0-8.20) in the study of Naidu et al. (20). The mean distance from the skull base was 0.36±0.70 mm (0-18, range: 0-3.8 mm) in this study. The

**Table 1. Correlation analysis of the distance of the anterior ethmoidal artery from the skull base and the depths of the olfactory fossa**

| | DOF (mm) | | AEA (mm) | |
|---|---|---|---|---|
| | r | p | r | p |
| Age | 0.197 | **0.014** | 0.232 | **0.004** |
| DOF (mm) | | | 0.248 | **0.000** |

Spearman xorrelation AEA: Anterior ethmoidal artery, DOF: Depth of the olfactory fossa

**Table 2. Mean age and gender of NSD (+) (with nasal septal deviation) and NSD (-) (without nasal septal deviation) patients**

| | | NSD (-) | | NSD (+) | | p |
|---|---|---|---|---|---|---|
| | | Mean ± SD/(n, %) | Median | Mean ± SD/(n, %) | Median | |
| Age | | 6.74±3.85 | 6.00 | 8.24±4.11 | 8.00 | **0.035**[m] |
| Gender | Female | 30 (49.2%) | | 51 (53.7%) | | 0.583[χ²] |
| | Male | 31 (50.8%) | | 44 (46.3%) | | |

[χ²]Chi-square test, [m]: Mann-Whitney U test, NSD: Nasal septal deviation, SD: Standard deviation

**Table 3. Depths of the olfactory fossa and distance of the anterior ethmoidal artery from the skull base for both sides of each (right and left) side of nasal septal deviation**

| | | Left side NSD | | Right side NSD | | p |
|---|---|---|---|---|---|---|
| | | Mean ± SD | Median | Mean ± SD | Median | |
| Age | | 8.65±4.01 | 8.00 | 7.68±4.24 | 6.00 | 0.193[m] |
| Gender | Female | 30 (54.5%) | | 21 (52.5%) | | 0.844[χ²] |
| | Male | 25 (45.5%) | | 19 (47.5%) | | |
| AEA-R (mm) | | 0.50±0.75 | 0.00 | 0.34±0.81 | 0.00 | 0.075[m] |
| AEA-L (mm) | | 0.32±0.54 | 0.00 | 0.44±1.05 | 0.00 | 0.400[m] |
| DOF-R (mm) | | 4.70±1.87 | 4.50 | 4.24±2.02 | 3.80 | 0.195[m] |
| DOF-L (mm) | | 4.35±1.74 | 4.20 | 4.63±2.56 | 3.85 | 0.955[m] |

[χ²]: Chi-square test, [m]: Mann-Whitney U test, AEA: Anterior ethmoidal artery, DOF: Depth of the olfactory fossa, SD: Standard deviation, NSD: Nasal septal deviation

**Table 4. Mean distances of AEA to the skull base of Keros types**

| | | Keros type 1 | Keros type 2 | Keros type 3 | p |
|---|---|---|---|---|---|
| AEA (mm) | Mean ± SD | 0.21±0.57 | 0.44±0.76 | 0.71±0.73 | **0.001**[K] |
| | Median | 0.00 | 0.00 | 0.70 | |

[K]: Kruskal-Wallis (Mann-Whitney U test), AEA: Anterior ethmoidal artery, SD: Standard deviation

difference from the literature in the mean distance of the AEA to the skull base in our population might be related to the age distribution and therefore the higher incidence of the skull base coursing of AEA. We also obtained a significant ($p<0.05$) positive correlation between age and the distance of AEA to the skull base, supporting this claim. We can assume that we may see the skull base course of AEA more frequently at an early age because of the ongoing process of the development of the skull base and ventilation of the paranasal sinuses in children.

Patients with a higher DOF are defined as having a higher accidental injury risk during surgery (12). It has been emphasized that the relationship between the olfactory fossa and AEA may be related to the intraoperative bleeding risk profile (3). In this study and the literature, both the distance of the AEA to the skull base and DOF increase with age, supporting that the development of the AEA trace and DOF are correlated with each other (1,3,31). DOF could be a reliable predictor of the course of AEA at the ethmoid roof (10,32). The relationship between the DOF and the location of the AEA was found to be significant ($p=0.016$) (10). In the study of Poteet et al. (32), AEA was located below the skull base in 55% of Keros type 3 cases, 29.5% of Keros type 2 cases, and 0% of Keros type 1 cases. In addition, the distance of the AEA from the skull base was significantly higher in Keros type 3 patients than in Keros type 2 patients (4.55 vs. 3.42 mm, $p=0.001$) (32). There was a positive correlation between DOF and the distance of the AEA trace from the skull base ($p<0.005$), in this study. The distance of the AEA course to the skull base was significantly higher in the Keros type 3 group (0.71±0.73) than in the Keros type 2 group (0.44±0.76) ($p<0.05$), and in the Keros Type 2 group than in the Keros Type 1 group (0.21±0.57) ($p<0.05$) (Table 4). These results show that with increasing DOF, the likelihood of the course of AEA within the ethmoid sinus increases.

NSD, particularly the high degrees, is a situation that challenges endoscopic sinus surgery. The nasal septum is also associated with the ethmoid roof; therefore, anterior skull base variations may be associated with NSD (33). Deviation was detected in 60.9% of our patients, and no significant gender difference was detected. However, the mean age of the patients with NSD was higher (8.24±4.11) than that of the patients without NSD (6.74±3.85) ($p=0.035$). Although nasal septal angulation can be observed in the embryological period, our results support the hypothesis that nasal septal angulation may continue in early childhood. When the right and left sides of the AEA-skull base distance and DOF values were evaluated separately according to the NSD side, no significant difference was detected (Table 3). However, it was noted that the AEA skull base distance and DOF were higher on the deviation side, although they did not reach statistically significant levels. We did not encounter any article in English comparing the course of AEA and nasal septal angulation in the literature. Onerci Altunay and Onerci (33) did not detect a significant difference in terms of cribriform depth ($p=0.713$) and Keros distribution ($p=0.514$) on the deviation side and the contralateral side. Bayrak et al. (34) and Özeren Keşkek and Aytuğar (35) also found no significant relationship between NSD and olfactory fossa depth ($p>0.005$).

### Study Limitations

This study has some limitations. Because this was a retrospectively planned study considering the effects of radiation on the pediatric population, the number of cases was limited and could not be increased. A single radiologist performed the measurements, and the intraobserver or interobserver variation was not examined.

## Conclusion

This study revealed age-related differences in the AEA course and the relationship of related structures such as the olfactory fossa and nasal septum with AEA. As the DOF increases, the AEA skull base distance also increases ($p<0.005$). In addition, both DOF ($p=0.014$) and AEA skull base distance ($p=0.004$) increase with age. We found that the age of the patients with NSD was higher than that of the patients without ($p=0.035$). Although no significant difference was detected in the AEA skull base distance or DOF on the NSD side, a slight increase in both AEA skull base distance and DOF was noted on the NSD side ($p>0.05$). These results show that olfactory roof anatomy and nasal septum deviation are not only related to the embryonic period but are also a process that continues after birth.

**Ethics Committee Approval:** The University of Health Sciences Turkey, İstanbul Training and Research Hospital Institutional Ethical Review Board approval was obtained for this study (approval number: 59, date: 10.03.2023).

**Informed Consent:** Retrospectively study.

**Financial Disclosure:** The author declared that this study received no financial support.

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İstanbul Med J 2024; 25(1): 72-6
**DOI:** 10.4274/imj.galenos.2024.59852

# Readmissions to Intensive Care from Palliative Care Units: Risk Factors, Incidence, and Outcome

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## ABSTRACT

**Introduction:** Palliative care units (PCUs), which offer medical, psychological, and physical support to patients in need of care, have become increasingly prevalent worldwide. A significant portion of the patient load in the PCU constitutes those transferred from the intensive care unit (ICU), yet a fraction of these patients are readmitted to the ICU for different reasons. It is a well-known fact that readmitted patients to the ICU exhibit higher morbidity and mortality.

**Methods:** Our study was designed retrospectively. Patients transferred from our hospital's ICU to the PCU were screened using our hospital's information system software dating back 10 years. Readmission to the ICU was defined as patients transferred from the ICU to the PCU and readmitted to the ICU within 72 h.

**Results:** Two hundred and seventy patients were included in the study. Of the 270 patients, 66 (24.4%) were readmitted to the İCU within 3 days. Logistic regression analysis was conducted to assess the risk factors for readmission to the ICU, which revealed that the use of home ventilators, high initial the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, presence of stroke, and vasoactive agent use during the hospital stay were independent risk factors for readmission to the ICU.

**Conclusion:** In patients transferred to palliative care following an ICU stay and readmitted to the ICU within 72 h, factors such as high APACHE II scores during admission, discharge with home ventilator, use of vasopressors in the ICU, intubation during ICU stay, and presence of stroke were identified as independent risk factors for readmission.

**Keywords:** Readmissions, intensive care units, palliative care, hospice care

## Introduction

Palliative care centers, which offer medical, psychological, and physical support to patients in need of care, regardless of whether they extend life expectancy or not, have become increasingly prevalent worldwide (1). In our country as well, palliative care units (PCUs) have been established for years, effectively providing care and palliation for patients. The concept of palliative care, as defined by the World Health Organization, involves an approach that enhances the quality of life for patients facing problems associated with life-threatening illnesses and their families through early diagnosis, comprehensive assessment, prevention, and alleviation of suffering by treating pain and other physical, psychological, and spiritual issues (2). However, globally, it has been reported that only approximately 14% of patients in need of palliative care can access palliative care facilities (3).

Patients can be transferred to PCUs from various hospital departments and from their homes. In our country, PCUs work as units that require continuous care for end-stage cancer patients, provide training for patient relatives, and aim to ensure that patients and their relatives adapt to the process before discharge home. A significant portion of the patient load in PCUs constitutes those transferred from intensive care units (ICUs), yet a fraction of these patients are readmitted to the ICU for different reasons. Readmissions to intensive care have been recommended as a quality criterion for countries and ICUs in numerous studies (4,5). Because of the above-mentioned reasons, clinicians might adopt a more cautious and protective approach during intensive care discharges. Similarly, tools are being developed to identify patients at an increased risk of readmission (6,7).

It is a well-known fact that readmitted patients to the ICU exhibit higher morbidity and mortality (7-9). In addition, these patients significantly increase hospital costs. Readmissions to intensive care have been studied multiple times, with reported frequencies ranging from approximately 1.2% to 14.5% (10-12). However, there are limited specific studies on patients transferred to PCUs. Moreover, globally, there is a new concept shaping the development of palliative care within intensive care and the adaptation of PCU fundamentals to ICUs. In our study, we aimed to investigate the risk factors, causes, and frequency of patients readmitted

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**Cite this article as:** Özkarakaş H, Öztürk MC. Readmissions to Intensive Care from Palliative Care Units: Risk Factors, Incidence, and Outcome. İstanbul Med J 2024; 25(1): 72-6.

**Received:** 08.01.2024
**Accepted:** 07.02.2024

to the ICU within three days after being transferred from the 3rd level ICU to the PCU.

## Methods

Our study was designed retrospectively at University of Health Sciences Turkey, İzmir Bozyaka Training and Research. Patients transferred from University of Health Sciences Turkey, İzmir Bozyaka Training and Research's 2nd and 3rd level ICUs to the PCU were screened through University of Health Sciences Turkey, İzmir Bozyaka Training and Research's information system software dating back 10 years. The study was approved by the University of Health Sciences Turkey, İzmir Bozyaka Training and Research Ethics Committee (approval number: 2023/182, date: 18.10.2023).

Data regarding patients were compiled by scanning both the hospital information system program and patient records. Our intensive care service is a multidisciplinary unit managed 24/7 by at least one intensive care specialist or anesthesiology and reanimation specialist, comprising 17 beds, with 10 in the 3rd level and 7 in the 2nd level.

Patients over 18 years of age admitted to the ICU for any reason were included. Patients diagnosed with cancer, those with pregnancy, and those admitted due to coronavirus disease-2019 (COVID-19) concerns were excluded because their inclusion could impact the results. Readmission to intensive care was defined as patients transferred from the ICU to the PCU and readmitted to the ICU within 72 h without a new pathology being detected. Data recorded included patients' admission diagnoses, comorbidities, previous units of admission, laboratory findings, the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, discharge status (survival or exitus), mechanical ventilator needs during intensive care stay, use of vasopressors throughout their stay, and requirements for blood transfusion and blood sugar imbalance (defined as the need for at least one intervention per day). In addition, the presence of tracheostomy upon referral to the PCU, discharge with a home ventilator, and the day and time of patient transfers were noted. Weekdays from Monday to Thursday were categorized as weekdays, whereas Friday to Sunday were considered weekends. Working hours were defined as 08.00-16.00 and non-working hours as 16.00-08.00.

### Statistical Analysis

IBM SPSS 22.0 (IBM Corp, Somers, NY, USA) was used for statistical analysis. The normal distribution of data was evaluated using the Kolmogorov-Smirnov test. Normally distributed continuous data were compared using independent sample t-tests and presented as mean ± standard deviation. Non-normally distributed data were presented as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical data were expressed as counts (n) and percentages (%) and compared using pearson's chi-square or Fisher's exact test. Data were analyzed at a 95% confidence level, with significance at $p<0.05$. Univariate logistic regression analysis was conducted to determine the variables associated with readmission to intensive care and in-hospital mortality. Multivariate logistic regression analysis was performed including all variables with $p<0.05$ in univariate analysis, applying backward elimination procedures to obtain adjusted odds ratios with 95% confidence intervals and identify variables independently associated with readmission to intensive care.

## Results

Throughout the duration of the study, 334 patients were transferred from the ICU to the PCU. However, because of inaccessible files for 24 patients and exclusion of 32 patients transferred to the palliative unit because of cancer diagnosis and 8 because of COVID-19, 270 patients were included in the study. Of the 270 patients, 66 (24.4%) were readmitted to the ICU within 3 days. The number of female patients was 114, whereas the number of male patients was 156 ($p=0.886$). The median (IQR) age for readmitted patients was 78.5 (11) compared to 69 (17) for non-readmitted patients. Among the reasons for intensive care admission, 112 patients were admitted most frequently because of respiratory problems; the second most common reason was neurological diseases (Table 1).

The APACHE II score median (IQR) 28 (4) for the readmitted group, whereas it was 20 (4) for the non-readmitted group ($p<0.001$). The Glasgow Coma Scale scores during intensive care admission were median 9 (6) for the readmitted group and 11 (4) for the non-readmitted group ($p<0.001$). Upon examination of patient comorbidities, statistical differences were found among factors such as vasopressor use, presence of multiple comorbidities, receiving renal replacement therapy during admission, use of blood products, and home ventilator use (Table 2).

Logistic regression analysis was conducted to assess the risk factors for readmission to the ICU, which revealed that the use of home ventilators, high initial APACHE II score, presence of stroke, and vasoactive agent use during the hospital stay were independent risk factors for readmission to the ICU (Table 3).

## Discussion

In our study, factors such as high APACHE II score during admission, discharge with home ventilator, vasopressor use during ICU stay, intubation during ICU stay, and presence of stroke were identified as independent risk factors for readmission to the ICU from the PCU. Furthermore, we observed a significantly higher mortality rate and longer hospital stay in the readmission group than in the non-readmission group.

PCUs are relatively new departments in our country. Since 2010, PCUs have been recognized as a medical discipline by the Ministry of Health of the Republic of Turkey, and their number and standards have gradually increased since this year (13). In addition to end-stage cancer patients in our country, it serves various patient populations, from bedridden patients who cannot take care of themselves and their families to patients with chronic diseases and education requirements. In addition, they have undertaken a higher burden compared to many other countries because it is a discipline in which the care of patients who do not need intensive care and will be discharged, especially those in need of care, the education of patients and their relatives, psychological support, and pain palliation.

Previous studies on ICU readmissions have reported rates ranging from 1.2% to 14.5% (10-12). However, our study showed a readmission rate

of 24.4%. We believe that the primary reason for our higher rate lies in our focus on patients solely transferred to and readmitted from the PCU. The majority of patients referred to the PCU had one or more additional comorbidities, a relatively higher average age compared with other studies, and incurable or life-limiting illnesses, which could have contributed to these outcomes.

Studies have demonstrated higher mortality rates among patients readmitted to the ICU. In previous studies, the mortality rate in patients with readmission to intensive care was found to be 12%-58% (14-16), and it was reported that there was a 4-11-fold increase in patients with readmission compared with patients without readmission (5,8,17). Similarly, we observed higher mortality in the readmission group

**Table 1. Characteristics of the study participants**

| | Non-readmitted | Readmitted | p-value |
|---|---|---|---|
| Gender F/M, (n) | 87/117 | 27/39 | 0.886 |
| Age[1] | 69 (17) | 78.5 (11) | 0.003 |
| APACHE II[1] | 20 (4) | 28 (4) | <0.001 |
| GKS[1] | 11 (4) | 9 (6) | <0.001 |
| **ICU admission disease n (%)** | | | 0.066 |
| Respiratuary diseases | 91 (44.6) | 21 (31.8) | |
| Sepsis | 18 (8.8) | 9 (13.6) | |
| Acute stroke | 41 (20.1) | 9 (13.6) | |
| Gastrointestinal diseases | 14 (2) | 5 (7.6) | |
| Renal diseases | 9 (4.4) | 6 (9.1) | |
| Trauma | 24 (11.8) | 9 (13.6) | |
| Postoperative | 14 (6.9) | 4 (6.1) | |
| Post-CPR | 3 (1.5) | 3 (4.5) | |
| **Comorbidities n (%)** | | | |
| Diabetes mellitus | 51 (25) | 21 (31.8) | 0.337 |
| Alzheimer's/demantia | 48 (23.5) | 23 (34.8) | 0.078 |
| Hypertension | 84 (41.4) | 33 (50) | 0.253 |
| Cardiological diseases | 48 (23.5) | 18 (27.3) | 0.621 |
| Hematologic diseases | 3 (1.5) | 3 (4.5) | 0.158 |
| COPD | 33 (16.2) | 6 (9.1) | 0.226 |
| Stroke | 57 (27.9) | 30 (45.5) | 0.010 |

[1]: Median (interquartile range), n: Count, F: Female, M: Male, ICU: Intensive care unit, GCS: Glasgow Coma Scale, APACHE II: Acute Physiology and Chronic Health Evaluation II, COPD: Chronic Obstructive Pulmonary Disease

**Table 2. Factors associated with readmission**

| | Non-readmitten | Readmitted | p-value |
|---|---|---|---|
| Weekdays/weekend discharge, (n) | 162/42 | 49/17 | 0.394 |
| Working hours/nightime discharge, (n) | 183/21 | 55/11 | 0.189 |
| Vasopressors (n, %) | 20 (9.8) | 32 (48.5) | <0.001 |
| RRT (n, %) | 12 (5.9) | 18 (27.3) | <0.001 |
| Blood transfusion (n, %) | 11 (5.4) | 8 (12.1) | 0.063 |
| Blood sugar imbalance | 63 (30.9) | 27 (40.9) | 0.137 |
| **Additional disease (n, %)** | | | <0.001 |
| 1 | 105 (51.5) | 18 (27.3) | |
| 2 or more | 99 (48.5) | 48 (72.7) | |
| Homevent (n, %) | 27 (13.2) | 30 (45.5) | <0.001 |
| Entubation[2] (n, %) | 114 (55.9) | 51 (77.3) | 0.002 |
| Leght of hospital stay[1] | 17 (19) | 30 (21) | <0.001 |
| Exitus (n, %) | 44 (21.6) | 31 (47) | <0.001 |

[1]: Median (interquartile range), [2]: Intubation history in the intensive care unit, n: Count, RRT: Renal replacement therapy

**Table 3. Multivariable logistic regression analysis**

| | Beta | Wald | p | OR | OR 95% safety margin |
|---|---|---|---|---|---|
| Age | 0.003 | 0.049 | 0.825 | 1.003 | 0.977-1.038 |
| GKS | 0.140 | 2.077 | 0.150 | 1.150 | 0.951-1.391 |
| APACHE II | 0.442 | 34.117 | <0.001 | 1.556 | 1.341-1.804 |
| Homevent | 2.101 | 12.083 | 0.001 | 8.177 | 2.501-26.739 |
| Stroke | 1.251 | 6.608 | 0.010 | 3.492 | 1.346-9.061 |
| Additional disease | 0.876 | 3.397 | 0.065 | 2.401 | 0.946-6.093 |
| Vp | 2.083 | 16.911 | <0.001 | 8.027 | 2.975-21.660 |
| RRT | 0.542 | 0.621 | 0.431 | 1.720 | 0.447-6.622 |
| Entubation | -1.193 | 3.032 | 0.082 | 0.303 | 0.079-1.162 |

OR: Odds ratio, GKS: Glasgow Coma Scale, APACHE II: Acute Physiology and Chronic Health Evaluation II, Vp: Vasopressor, RRT: Renal replacement therapy

compared with the other group in our study. Additionally, our observed rate was higher than that reported in other literature, possibly due to the specific focus of our study on a distinct group. This underscores the importance of identifying patients at risk of readmission during ICU discharge. Identifying and mitigating these risks beforehand could limit readmissions, ensure maximum coordination among healthcare providers for the continuation of treatment, and enhance healthcare quality.

Our study revealed that patients requiring respiratory support systems were readmitted to the ICU more frequently. Similar studies have highlighted respiratory diseases and failure as significant risk factors for readmission (18,19). In contrast to other studies, we found that the use of home ventilator support and tracheostomy triggered more frequent readmissions. This suggests that patients with tracheostomy and home mechanical ventilator support carry additional risks compared with others and are more prone to acute complications.

Another finding of our study was that readmitted patients had longer hospital stays. This may significantly increase per-patient costs. Previous studies have also observed increased hospital costs in patients with ICU readmission (7,11,20,21). A more systematic approach to ICU discharges, inter-team coordination, and minimizing factors leading to readmission could limit the risk of readmission and better use hospital and economic resources.

In our study, more readmissions were observed in the group receiving vasopressors and having infectious diseases (pneumonia, sepsis, etc.) during hospitalization in the ICU. In a study conducted by Öngel Çayören et al. (19) in Turkey, a high Sequential Organ Failure Assessment score at any time during hospitalization was found to be a risk factor for readmission. Our results support this finding.

In our study, high APACHE II scores were identified as independent risk factors for high readmission risk. Several studies evaluating ICU readmission have similarly found high disease severity scores as an independent risk factor for readmission, consistent with our findings (7,11,20,22-24).

### Study Limitations

Our study has some limitations. First, it was a single-center study. While it is challenging to estimate the impact of a larger multi-center cohort on outcomes, we believe that similar results can be obtained. Second, our study was retrospective, and the third limitation is that PCUs and patient populations may differ across countries, which unfortunately our study overlooks.

## Conclusion

In patients transferred to palliative care following an ICU stay and readmitted to the ICU within 72 h, factors such as high APACHE II scores during admission, discharge with home ventilator, use of vasopressors in the ICU, intubation during ICU stay, and presence of stroke were identified as independent risk factors for readmission. Additionally, the mortality rate and hospital stay were significantly higher in the readmission group than in the non-readmission group. Formun Üstü

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Turkey, İzmir Bozyaka Training and Research Ethics Committee (approval number: 2023/182, date: 18.10.2023).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Surgical and Medical Practices - H.Ö.; Concept - H.Ö., M.C.Ö.; Design - H.Ö., M.C.Ö.; Data Collection or Processing - H.Ö., M.C.Ö.; Analysis or Interpretation - H.Ö.; Literature Search - M.C.Ö.; Writing - H.Ö., M.C.Ö.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 77-83
**DOI:** 10.4274/imj.galenos.2024.75332

# Medical Students' Experiences and Factors Related to Their Motivation for Undergraduate Courses Involving Scientific Research

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## ABSTRACT

**Introduction:** The aims of this study were to investigate the perceptions of faculty of medicine students about conducting scientific research and to identify the factors influencing their motivation to conduct scientific research.

**Methods:** This cross-sectional study involved 543 students from the second to fifth grades at the faculty of medicine. The questionnaire included questions about career plans, experiences with research courses, and factors affecting students' motivation to conduct research.

**Results:** Clinical semester students are more likely to present their research at congresses (p=0.001) and to publish their work nationally (p=0.001) and internationally (p=0.014) compared with preclinical semester students. Preclinical period students showed greater agreement than clinical period students in their belief that their motivation for conducting research would be higher by involving them in the decision-making process for selecting research topics (p=0.013) and by streamlining the ethics committee approval process (p=0.004). Students in the clinical group were more motivated when their opinions were considered in research design courses (p=0.043), when ample time was dedicated in the curriculum for research completion (p=0.001), and when time was allocated for interaction with advisors and peers (p=0.001).

**Conclusion:** This study suggests that incorporating compulsory, well-supported research activities that integrate evidence-based medicine and scientific research into pre-graduate medical education may encourage students to consider research careers. Student willingness to participate in research may be enhanced when their research subject preferences and original ideas are considered, adequate time for research is provided, group work is encouraged, and effective counseling is available.

**Keywords:** Medical education, program development, research, medical students, curriculum

## Introduction

Within the scope of evidence-based medicine practices, the necessity for medical school graduates to know scientific research methods and to perform effective practices is widely accepted (1-4). It is necessary to strengthen students' interest in research during their medical school education. Considering that the number of physician-scientists is decreasing (5-7) and that measures should be taken in this regard (6,7), it is important to understand the perceptions of medical students toward conducting scientific research, their experiences related to the education they received on this subject, and especially their motivation.

An individual's motivation can be related to many personal and environmental factors, such as autonomy in the sense of feeling that one has a choice and willingly approves of one's behavior, competence in the sense of feeling mastery and being effective in one's activities, and relatedness in the sense of feeling connected to others and belonging, as proposed in self-determination theory (1,2,8,9). It is important to understand how much the education program enables the acquisition of scientific method and research competence, how students perceive their experiences in the program, and how they evaluate the motivating and non-motivating situations related to the program to revise the education programs in line with student needs. It should be understood what changes occur in students' motivation in different educational periods and which types of motivation come to the fore in which periods (1,2). With this evidence, educational programs can be shaped to be more effective (4,5,7-9).

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**Cite this article as:** Demir A, İnanıcı SY. Medical Students' Experiences and Factors Related to Their Motivation for Undergraduate Courses Involving Scientific Research. İstanbul Med J 2024; 25(1): 77-83.

**Received:** 31.01.2024
**Accepted:** 11.02.2024

This study investigates, define, and explain the factors that motivate medical students to conduct scientific research. Accordingly, the research problems of this study are as follows:

1. What are the students' views on the factors that may affect their motivation for research in relation to the educational program?

- In which ways do opinions on factors that may affect research motivation differ between clinical and preclinical period students?

2. What are the students' course experiences in designing and managing scientific research?

- How do students' course experiences in designing and managing scientific research differ between clinical and preclinical students?

## Methods

### Participants and the Data Collection Instrument

The study was a cross-sectional study conducted with 543 students in the 2nd on 5th grades of our faculty of medicine using a face-to-face questionnaire collection method. The participation rate was 67%, and the students were selected using a convenient sampling method. After the purpose of the study was announced to them face-to-face and consent was obtained, the volunteer students filled out the forms themselves in their learning environments. The questionnaire used in the study was created by the researchers and includes the following headings: demographic data, academic plans to conduct scientific research, research experiences at the faculty of medicine, opinions on the part of the curriculum related to scientific research, and factors that may be related to motivation to conduct scientific research. Exclusion criteria were not volunteering to participate in the study, transferring from another university to the fourth and/or fifth year, and incomplete answers to the questionnaire.

### Context in Which the Research was Conducted

In our education program, scientific research methods and practices are conducted as a vertically integrated program, Introduction to Clinical Practice (ICP), which covers the first three years of education, and an evidence-based medicine program in the fifth year. In addition to taking theoretical courses on the subject, each year, students conduct scientific research in peer groups of 5-6 students under the supervision of a faculty member. The products of these studies are presented orally or as posters at the national Marmara Student Congress (MaSCo), which is organized with the contributions of volunteer students and the faculty members they voluntarily consult. Students' research reports and individual performances during the year are evaluated by their advisors and program coordinators.

The study was conducted in accordance with the Declaration of Helsinki with the permission of Marmara University Faculty of Medicine Ethics Committee (protocol code: 09.2019.1046, date: 06.12.2019).

### Statistical Analysis

The data obtained from the questionnaire were analyzed using the Jamovi 2.3.21 program. Mean, standard deviation, median, and frequency distributions were used for statistical analysis. Chi-square analysis and Mann-Whitney U test were used for comparisons, and significance value was taken as $p<0.05$.

## Results

### General Data of the Participants

The mean age of the 543 students participating in the study was 21.6±1.6 years and 57.3% (n=310) were female. Table 1 shows the participants' career planning intentions. When asked to evaluate the importance given to scientific research skills at MUSTF in general, 20.6% (n=111) of the participants stated that it was extremely important, 50.2% (n=270) critical, and 23.2% (n=125) moderately important. The rate of those who said that this issue was not given any importance or some importance was 6% (n=32). Of the students, 20.7% (n=111) reported that they voluntarily participated in scientific research outside the compulsory courses at the faculty of medicine. Of those who voluntarily participated in a scientific study, 19.3% (n=21) reported that they had to leave the study at the end of the study. While 39.9% (n=210) of the participants reported that they would definitely participate in an elective course/internship to improve their research skills, 48.1% (n=253) were undecided and 12% (n=63) stated that they would definitely not choose this course/internship.

The status of students regarding the products of scientific research in which they compulsorily or voluntarily participated during their education at the Faculty of Medicine is as follows: 34.6% (n=183) reported that their research was presented as a paper in a congress other than MaSCo, 16.8% (n=88) published articles in national journals, and 13.2% (n=69) published articles in international journals.

Table 2 shows the extent to which the participants agree with the statements that include several variables that may be related to the motivation to conduct scientific research. Table 3 shows the evaluations made by the students considering the courses (ICP research, elective courses, etc.) they are taking at our medical faculty that involve planning, conducting, and evaluating scientific research.

### Analyses of the Participants' Data According to Their Education Periods

Of the participants, 365 were preclinical semester students (2nd grade: 182 and 3rd grade: 183) and 178 were clinical semester students (4th

**Table 1. Participants' career planning intentions**

| Questions | I don't think about it at all | | I am not sure | | I definitely think (d) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Intention to conduct scientific research when starting medical school | 108 | 19.9 | 184 | 33.9 | 250 | 46.1 |
| Planning to study abroad for a specialization/academic career | 34 | 6.3 | 147 | 27.1 | 362 | 66.7 |
| Plans to pursue an academic career (e.g. conducting and publishing research after faculty, becoming an associate professor or professor) | 52 | 9.6 | 156 | 28.8 | 334 | 61.6 |

grade: 56 and 5th grade: 122). Gender distribution ratios did not differ significantly by semester (p=0.354). Clinical semester students found their English language proficiency higher than that of preclinical semester students in terms of both reading/understanding articles and presenting scientific research orally (Table 4).

The importance given to scientific research skills in the MITF curriculum was found to be higher in preclinical period students than in clinical period students (p=0.032). 72.8% (n=249) of preclinical students and 70.7% (n=116) of clinical students did not take part in scientific research before starting medical school (p=0.672). The rate of voluntary participation in a scientific study other than compulsory courses was higher in clinical semester students (34.1%, n=60) than in preclinical semester students (14.1%, n=51) (p=0.001). Among those who voluntarily participated in scientific research, the rate of dropout before the end of the study was 10.2% (n=5) for the preclinical period and 26.7% (n=16) for the clinical period (p=0.049). The responses did not differ by semester in terms of whether the students would prefer an elective course/internship to improve their scientific research skills (p=0.555).

Table 5 shows the results of the studies conducted by the students during their medical education according to the semesters. Clinical semester students are more likely to present their research results orally at a congress other than MaSCo (p=0.001), to publish national (p=0.001) and international (p=0.001) articles than preclinical semester students.

When the participants were asked to what extent they agreed with some variables that may be related to the motivation to conduct a scientific research, the students in the preclinical group agreed more strongly with the statement that "Making a joint decision by taking my preference into consideration while determining the research topic increases my willingness to conduct research" (p=0.013) and "Facilitating the Ethics Committee Approval process increases the willingness to participate in research" (p=0.004) than the students in the clinical group.

The evaluations of the groups based on the scientific research courses they were taking at our medical faculty were compared according to semesters. Students in the clinical group were more likely to agree than students in the preclinical group with the statements that students' opinions were given importance in the management of the research process (p=0.043), sufficient time was allocated in the program for the

**Table 2. Variables related to participants' motivation to conduct scientific research**

| Questions | Strongly disagree | | Disagree | | Undecided | | I agree | | Totally agree | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Making a joint decision by taking my preferences into consideration when determining the research topic increases my willingness to conduct research. | 4 | 0.7 | 15 | 2.8 | 18 | 3.3 | 217 | 40.3 | 285 | 52.9 | 539 | 100 |
| Being able to meet regularly with my research advisor increases my willingness to participate in research. | 1 | 0.2 | 13 | 2.4 | 22 | 4.1 | 185 | 34.4 | 317 | 58.9 | 538 | 100 |
| Facilitating the Ethics Committee Approval process increases the willingness to participate in research | 5 | 0.9 | 13 | 2.4 | 27 | 5.0 | 142 | 26.4 | 351 | 65.2 | 538 | 100 |
| Providing research support/scholarship increases my willingness to participate in research. | 6 | 1.1 | 6 | 1.1 | 36 | 6.7 | 112 | 21.0 | 374 | 70.0 | 534 | 100 |
| The opportunity to conduct research in the field in which I want to advance in my career increases my desire to conduct research. | 2 | 0.4 | 11 | 2.0 | 20 | 3.7 | 117 | 21.7 | 388 | 72.1 | 538 | 100 |
| Research is advantageous for a medical career. | 2 | 0.4 | 12 | 2.3 | 40 | 7.5 | 151 | 28.3 | 328 | 61.5 | 533 | 100 |
| It is difficult to combine a research career with a clinical career. | 13 | 2.5 | 46 | 8.7 | 159 | 30.1 | 183 | 34.6 | 128 | 24.2 | 529 | 100 |
| Conducting research while studying is only an option for students who want a successful, elite, andacademic career. | 80 | 15.0 | 196 | 36.6 | 124 | 23.2 | 74 | 13.8 | 61 | 11.4 | 535 | 100 |
| Providing statistics training as part of the training increases my willingness to participate in research | 29 | 5.4 | 67 | 12.5 | 126 | 23.5 | 166 | 30.9 | 149 | 27.7 | 537 | 100 |
| Receiving regular feedback on the progress of my ability to conduct research increases my desire to conduct research. | 3 | 0.6 | 11 | 2.1 | 69 | 12.9 | 228 | 42.5 | 225 | 42.0 | 536 | 100 |
| When the research is completed, the feeling of accomplishment makes me want to conduct more research. | 5 | 0.9 | 13 | 2.4 | 35 | 6.5 | 159 | 29.7 | 324 | 60.4 | 536 | 100 |
| Conducting the research as a group with friends makes me enjoy the research process more. | 29 | 5.4 | 43 | 8.0 | 91 | 17.0 | 172 | 32.1 | 201 | 37.5 | 536 | 100 |
| Having people around me who are role models for research (family members, educators, counselors, etc.) increases my desire to conduct research. | 5 | 0.9 | 11 | 2.0 | 46 | 8.5 | 177 | 32.8 | 300 | 55.7 | 539 | 100 |
| The idea that I can contribute to scientific knowledge by conducting research increases my desire to conduct research. | 9 | 1.7 | 18 | 3.4 | 58 | 10.8 | 191 | 35.6 | 261 | 48.6 | 537 | 100 |
| Identifying with a research career and conducting research with a higher sense of purpose, such as the pursuit of scientific knowledge, increases my desire for research. | 11 | 2.1 | 21 | 3.9 | 81 | 15.1 | 182 | 34.0 | 241 | 45.0 | 536 | 100 |

processes related to the completion of the research (p=0.001), time was allocated in the training program especially for the interaction of students in the group and students and advisors (p=0.001), and participation in MaSCo supported the student's self-confidence in the subject (p=0.009).

## Discussion

### Career Plans and Mandatory Research Activities

One of the common aspects touched upon by medical education studies is the interest and positive attitude expressed by medical students toward research (1,2,7,10). In this study, approximately half of the students reported that they intended to conduct scientific research when they entered the faculty, and two-thirds of them even reported that they aimed to pursue an academic career. In this sense, knowing the career plans and profiles of students regarding scientific research at the time they entered the faculty is important to support the motivation and competencies to conduct scientific research in the education program and to implement practices that increase the motivation, knowledge, and practice of those who have deficiencies in this regard (3,7,10-12). Rosenkranz et al. (1) reported that students who completed a compulsory research project significantly increased their intention to conduct research in the future. As stated in the review of Stone et al. (7), the number of physician scientists is decreasing, and to prevent this, it is recommended to develop a national research program (13), encourage voluntary participation in research (14), and organize workshops and research courses (15). Studies have recommended mandatory research activities in the education programs of medical faculties (1,4,16). achieving the task of managing a compulsory research project at the faculty increases participation in elective activities related to the subject with the confidence it gives to the individual (1). In this study, more than half of the participants reported that being able to share their research products in a scientific environment increased their confidence and made them realize the importance of evidence-based medicine. More than two-thirds of the students who participated in the study are aware that specific applications with scientific content are important at the faculty. The results of the study show that the research products of the students are not limited to the national MaSCo in line with the practices that are compulsory in the faculty and cover both the clinical and preclinical period, but they also participate in congresses other than MaSCo, and even their studies are transformed into national and international publications. It has been reported that the involvement of medical students in scientific research occurs mostly during their connection with clinical practice (1,2,17,18). As reported in other studies, it was observed in our study that students were more involved in scientific research in the clinical practice environment. In particular,

**Table 3. Please indicate to what extent you agree with the following statements considering the courses you have taken at the faculty of medicine (research, elective courses, etc.) that include planning, conducting, and evaluating scientific research**

| Questions | None | | A little bit | | Middle | | Quite a lot | | Extremely | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| Our ideas about what/how we want to conduct the research are valued. | 25 | 4.6 | 48 | 8.9 | 167 | 30.8 | 208 | 38.4 | 94 | 17.3 | 542 | 100 |
| Sufficient time is given for planning the research, reviewing the literature, and managing the process. | 33 | 6.1 | 67 | 12.4 | 180 | 33.3 | 185 | 34.2 | 76 | 14.0 | 541 | 100 |
| When planning and conducting a research project, sufficient time is given for students to discuss and exchange ideas among themselves and with the supervisor. | 19 | 3.5 | 84 | 15.5 | 164 | 30.3 | 195 | 36.0 | 79 | 14.6 | 541 | 100 |
| During research planning and execution, no matter how senior, experienced, etc. the consultant may be, we are made to feel that we are equal to those conducting the research. | 45 | 8.3 | 74 | 13.7 | 136 | 25.1 | 177 | 32.7 | 109 | 20.1 | 541 | 100 |
| During the Medical Student Congress, students' self-confidence and awareness of the importance of evidence-based medicine increased with the inclusion of oral presentations, poster preparation, and research. | 19 | 3.5 | 40 | 7.4 | 105 | 19.4 | 201 | 37.2 | 175 | 32.4 | 540 | 100 |
| Gaining experience of working in a group and seeing the positive and negative aspects of working in a group contributes to participation in future teamwork environments. | 7 | 1.3 | 27 | 5.0 | 69 | 12.8 | 223 | 41.2 | 215 | 39.7 | 541 | 100 |
| The fact that the group members in the research group do not support the study at the same level reduces my motivation to work. | 12 | 2.2 | 26 | 4.8 | 55 | 10.2 | 125 | 23.1 | 323 | 59.7 | 541 | 100 |
| The pressure of grades in this program puts stress on us. | 15 | 2.8 | 27 | 5.0 | 87 | 16.3 | 127 | 23.7 | 279 | 52.1 | 535 | 100 |
| In the research planning/execution/interpretation stages, we receive suggestions and encouragement from the advisor at points where we are not organized or do not know what to do. | 25 | 4.6 | 67 | 12.5 | 127 | 23.6 | 183 | 34.0 | 136 | 25.3 | 538 | 100 |
| I think the senior people with whom we conducted the research generally empathized with us about what we went through during the research process. | 56 | 10.4 | 103 | 19.1 | 142 | 26.3 | 135 | 25.0 | 103 | 19.1 | 539 | 100 |
| The person advising, who is senior in research, explains to us the logic of what he/she is asking/recommending. | 28 | 5.2 | 57 | 10.6 | 131 | 24.3 | 189 | 35.1 | 134 | 24.9 | 539 | 100 |
| We receive effective feedback on our progress in planning and conducting research. | 36 | 6.7 | 84 | 15.6 | 141 | 26.2 | 171 | 31.7 | 107 | 19.9 | 539 | 100 |

clinical semester students tend to carry out research projects outside the compulsory courses.

**Motivation to conduct scientific research:** Self-determination theory Kusurkar et al. (2) categorized motivational factors into those that can be manipulated by curriculum developers, including the concepts of autonomy, competence, and relatedness, and those that cannot be manipulated, such as gender, previous educational experience, and socio-economic status. Using the framework of these authors and Rosenkranz et al. (1), the study data related to students' motivation for research and their experiences in curriculum implementation can be interpreted as follows:

Mandatory research activities can be sustained by providing students with choices in selecting topics, advisors, and group members, and can be further enhanced through elective research opportunities (1). Providing such a choice by instructors or educational programmers can increase motivation by supporting the autonomy element of self-determination and support course-related competencies (2,9,19). In our study, especially the students in the preclinical group agreed more intensely with the idea that making a joint decision by considering the student's opinion while determining the research topic would increase their desire to do research. Students, with preclinical period students being more so, stated that their opinions on what/how to do during the research were given importance within the education program. The possibility of choice in the research curriculum should be carefully evaluated because such options, which sometimes contradict one another, can either enhance or limit students' skills, especially in realizing their needs for autonomy and competence (4,20,21). In our study, students stated that offering research opportunities suitable for the specialty they would like to choose in the future would increase their research motivation.

If scientific research is a part of the curriculum, the time limitation in the curriculum should be considered. Having a planned research calendar and following it is important in time management. In this study, approximately half of the participants strongly agreed that they were allocated enough time for the research planning process and for discussion with the group and the supervisor during the process. The training program may need to be revised to make room for such activities.

When the students' responses are evaluated, changes can be made in the program to balance external motivation. Many students found it motivating to facilitate the ethics committee approval process and to provide research award scholarships. In line with these expectations, the program could consider establishing a separate ethics committee commission that evaluates proposals for compulsory research courses. It may also be planned to provide students with additional counseling services that are more effective and supportive of their competencies, especially during the ethics committee application period. Students in the preclinical group were more likely to agree with this statement than those in the clinical group.

Many medical students may lack the ability to conduct research during their undergraduate education (7,22,23), and this deficiency may be associated with low motivation and low self-efficacy (22). Therefore, lack of experience and training on this subject are among the barriers to students' participation in research (1,7,10,24). In this study, the students' expectation of convenience may also be due to the fact that they do not find themselves competent in such bureaucratic procedures. On the other hand, most of the participants think that conducting scientific research is advantageous for a medical career despite the difficulties they may have experienced, and they do not believe that only a certain

**Table 4. Assessing the ability to use English for scientific purposes**

| Period | Preclinical period | | Clinical period | |
|---|---|---|---|---|
| **Reading/understanding articles** | **n** | **%** | **n** | **%** |
| Very weak | 3 | 0.8 | 2 | 1.1 |
| Weak | 16 | 4.4 | 4 | 2.3 |
| Middle | 89 | 24.5 | 21 | 11.9 |
| Good | 185 | 51.0 | 83 | 47.2 |
| Excellent | 70 | 19.3 | 66 | 37.5 |
| Total | 363 | 100 | 176 | 100 |
| U=24218.0, z=-4.93, p=0.001 | Median=4 | | Median=4 | |
| **Oral research presentation** | **n** | **%** | **n** | **%** |
| Very weak | 222 | 6.1 | 5 | 2.8 |
| Weak | 69 | 19.0 | 23 | 13.1 |
| Middle | 131 | 36.1 | 53 | 30.1 |
| Good | 98 | 27.0 | 63 | 35.8 |
| Excellent | 43 | 11.8 | 32 | 18.2 |
| Total | 363 | 100 | 176 | 100 |
| U=26238.0, z=-3.49, p=0.001 | Median=3 | | Median=4 | |

**Table 5. Products of students' work during their medical education by semester**

| Period | Preclinical period | | | | | | Clinical period | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | There is | | No | | Total | | There is | | No | | Total | |
| **Product** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Oral poster except for MaSCo | 101 | 28.5 | 253 | 71.5 | 354 | 100 | 82 | 46.9 | 93 | 53.1 | 175 | 100 |
| $X^2(1)=17.38$, p=0.001 | | | | | | | | | | | | |
| National article | 43 | 12.3 | 307 | 87.7 | 350 | 100 | 45 | 26.0 | 128 | 74.0 | 173 | 100 |
| $X^2(1)=15.58$, p=0.001 | | | | | | | | | | | | |
| International article | 37 | 10.6 | 313 | 89.4 | 350 | 100 | 32 | 18.5 | 141 | 81.5 | 173 | 100 |
| $X^2(1)=6.35$, p=0.014 | | | | | | | | | | | | |

MaSCo: Marmara Student Congress

group of students can conduct scientific research. In accordance with previous studies (7,25-28), we also found that receiving regular feedback and supporting the process with statistics courses were mostly motivating, but they believed that it was difficult to perform clinical work and research together.

Being able to work in a team is among the professional competencies that medical students need to develop. In the compulsory scientific research training program at the MUMF, students work in groups, performance evaluations are assessed both individually and as a group, and teamwork processes are supported in these practices. This structure is closely related to the relatedness element of self-determination theory: individuals go through a process in which they establish intense relationships with both their teammates and supervisors. In our study, as in other studies, most of the students reported that they enjoyed the research process more when the research was conducted with friends and that the group experience could contribute to future teamwork (1,4). On the other hand, the fact that the group members in the research group did not support the study at the same level decreased their motivation to study. At this point, it can be suggested that the contribution of each group member in the program should be evaluated by the advisor and its contribution to the final grade obtained from the course should be increased.

Increasing clinical interest and awareness of one's researcher identity can be accelerated by connecting with a person to whom the student can relate, such as a role model, mentor, or advisor (1,3,10,29). In the present study, students reported that the advisor explained the logic of what the students wanted to do and that they could get encouragement and suggestions from the advisor when they got stuck in the research process. On the other hand, only about half of the participants reported that they felt equal to their advisor in the process, that they felt that the advisor empathized with them, and that they were able to receive effective feedback on the process. In this respect, it may be considered to conduct qualitative studies to understand the reasons for the feeling of lack of empathy in the program and to support faculty members with training of trainers based on these findings.

## Conclusion

This study suggests that incorporating compulsory, well-supported research activities that integrate evidence-based medicine and scientific research into pre-graduate medical education may encourage students to consider research careers. Additionally, presenting their work at student congresses appears to increase their confidence and appreciation of the importance of evidence-based medicine. Student willingness to participate in research may be enhanced when their research subject preferences and original ideas are considered, adequate time for research is provided, group work is encouraged, effective counseling is available, and the Ethics Committee approval process is facilitated.

**Ethics Committee Approval:** The study was conducted in accordance with the Declaration of Helsinki with the permission of Marmara University Faculty of Medicine Ethics Committee (protocol code: 09.2019.1046, date: 06.12.2019).

**Informed Consent:** It was obtained.

**Authorship Contributions:** Surgical and Medical Practices - A.D., S.Y.İ.; Concept - A.D., S.Y.İ.; Design - A.D., S.Y.İ.; Data Collection or Processing - A.D., S.Y.İ.; Analysis or Interpretation - A.D., S.Y.İ.; Literature Search - A.D., S.Y.İ.; Writing - A.D., S.Y.İ.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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

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İstanbul Med J 2024; 25(1): 84-8
**DOI:** 10.4274/imj.galenos.2024.57527

# Association Between Plasma Grem1 and Peritoneal Permeability Alterations in Dialysis Patients

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## ABSTRACT

**Introduction:** Alterations in the peritoneal membrane can cause trouble for adequate dialysis. We proposed to evaluate a possible relationship between peritoneal permeability and Grem1 protein in peritoneal dialysis (PD) patients.

**Methods:** Adult PD patients who undergoing dialysis for at least one year were included. Grem1 level was measured in plasma. The peritoneal equalization test (PET) was used to define peritoneal transporting properties. Dialysate to plasma ratio for creatinine (DPRC) value was used as the parameter of the permeability. The first and last DPRC values were compared to determine membrane alteration status.

**Results:** A total of 60 patients were enrolled. The mean age was 52.9±14.3 years. The average PD duration was 60.3 (24-86.5) months. The average Grem1 level was 164.9 (81.6-164.9) ng/mL. An overall 5.8% increase was determined in DPRC value. There was no statistically significant difference in Grem1 levels between increasing DPRC and non-increasing DPRC groups (p=0.783). According to PET classification: class elevation was observed in 31.7% (19) patients. The plasma Grem1 levels of these groups are as follows: 204.2 ng/mL in stable patients, 168.2 ng/mL in ascending patients, and 196.2 ng/mL in descending patients. There was no statistically significant difference between the groups in terms of Grem1 levels in One-Way ANOVA (p=0.709).

**Conclusion:** We did not identify any correlation between changes in peritoneal permeability and plasma Grem1 levels. However, we have emphasized the importance of novel biomarkers that could predict the changes in peritoneal permeability.

**Keywords:** Grem1, dialysis, peritoneal membrane, permeability

## Introduction

Grem1 (Gremlin1) is a member of the antagonists of bone morphogenetic proteins (BMP) pathway. The gene encodes a Grem1 is located in 15q13.3 and has three exons. Grem1 is a 184-amino acid glycoprotein and a cysteine knot-secreted protein (1). The antagonistic effect of the secreted protein encoded by this gene is presumably via direct binding to BMPs (2). Furthermore, Grem1 is a cell growth and differentiation factor that plays a key role in embryogenesis. It can regulate organogenesis, organ embodiment, and tissue differentiation. Regulation of BMPs by Grem1 is also essential for kidney and lung development (3).

The transforming growth factor-beta (TGF-β) pathway is implicated as a driver of fibrosis-related diseases. BMP-7 has an antagonistic effect on TGF-β signaling (4). In addition, experimental studies revealed that Grem1 promoted the proliferation and activation of fibroblast cells by enhancing fatty acid oxidation (5). The contribution of Grem1 to fibrosis has been shown in several organs (3).

The peritoneum is used as a semipermeable membrane in peritoneal dialysis (PD). Solute diffusion and ultrafiltration (UF) occur through this membrane. Alterations in the peritoneal membrane, such as inflammation, neoangiogenesis, and fibrosis, cause trouble for adequate dialysis (6). Increased peritoneal permeability can particularly result in UF failure. TGF-β1-induced epithelial-to-mesenchymal transition (EMT) plays a crucial role in alterations of the peritoneal membrane. Moreover, mesenchymal Grem1-mediated BMP antagonism is required for proper epithelial- mesenchymal signaling (7).

BMP antagonism through Grem1 may affect the transport features of the peritoneal membrane in clinical practice. In addition, this antagonism has not been investigated sufficiently in PD practice. Therefore, this study aimed to evaluate a possible relationship between Grem1 and the permeability of the peritoneal membrane in patients with PD.

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**Cite this article as:** Uysal C, Gündoğdu A, Çifçi H, Koçyiğit İ. Association Between Plasma Grem1 and Peritoneal Permeability Alterations in Dialysis Patients. İstanbul Med J 2024; 25(1): 84-8.

**Received:** 07.01.2024
**Accepted:** 11.02.2024

## Methods

This study was designed as a single-center study. Patients enrolled between 01.01.2020 and 01.01.2021. The study was approved by the Erciyes University Ethics Committee (approval number: 2019/678, date: 09.10.2019). Written informed consent was obtained from the patients by explaining the procedure of the study. This clinical investigation was conducted in accordance with the Helsinki Declaration.

Key inclusion criteria were age ≥18 and should have maintained PD for at least one year. The patients were not included in the study during the active peritonitis period. The minimum duration since the patient last experienced peritonitis was three months for inclusion. Patients with leakage of dialysate, dysfunction of the PD catheter, cirrhosis, ascites, or systemic infection findings were excluded. Furthermore, patients who underwent abdominal surgery during the follow-up period were excluded from the study.

The peritoneal equalization test (PET) was used to define the transporting properties of the peritoneum. Standard PET was performed in this study as described by Twardowski (8). The patients were classified by the 4-h dialysate-to-plasma ratio (D/P) for creatinine. Four permeability groups were determined as follows: high, high average, low average, and low. Two PET values were compared for alterations in peritoneal membrane permeability. The initial PET was defined as performed when the patients started PD. The last PET was defined as performing concomitantly with Grem1 sampling. The D/P ratio for creatinine (DPRC) was used to calculate the alteration in peritoneal membrane permeability. 24-h urine and dialysate samples were used to calculate creatinine clearance. We used the International Society for Peritoneal Dialysis Guidelines for the diagnosis of peritonitis (9).

The Grem1 level was measured in plasma. Venous blood samples were centrifuged for 10 min at 5000 rpm (NF 400 centrifuges, Turkey). The samples were preserved at -80 °C until assessment. Grem1 levels were measured using commercially available ELISA kits (Elabscience Biotechnology Inc., Houston, TX, USA), according to the manufacturer's instructions and expressed as ng/mL. The detection range of the kits for Grem1 was 0.16-10 ng/mL. The inter-assay coefficient of variation for the kits was <10%.

### Statistical Analysis

The normality of the data was tested with the Shapiro-Wilk test; (q-q) and histogram plots. The Shapiro-Wilk test was employed to assess whether the numerical data followed a normal distribution. Numerical data showing a normal distribution are presented as mean ± standard deviation, whereas non-normally distributed numerical data are presented as median ($1^{st}$-$3^{rd}$ quartiles). Non-numerical (categorical) data are expressed as percentages. Statistical evaluations between the two periods were performed using the paired t-test for normally distributed parameters. Mann-Whitney U was used to compare the medians of non-normally distributed parameters. The relationships between categorical variables were tested using the chi-square test. ANOVA was used to determine differences between research results from three or more unrelated samples or groups. Data analysis was conducted using TURCOSA (Turcosa Analytics Ltd Co, Turkey, www.turcosa.com.tr) statistical software. The significance level was set as $p<0.05$.

## Results

In this study, 60 patients were enrolled and analyzed. The patients consisted of 31 females (51.7%) and 29 males (48.3%). The mean age of patients was 52.9±14.3 years. The median plasma Grem1 level of the patients was 164.9 (81.6-164.9) ng/mL. Demographic features and laboratory results of the patients are summarized in Table 1.

The distribution of patients according to the PD modality was as follows: 80% (n=48) continuous ambulatory peritoneal dialysis and 20% (n=12) automated peritoneal dialysis. The median PD duration of the patients was 60.3 (24-86.5) months. The median Kt/V urea was 2.02 (1.82-2.23). The median creatinine clearance was 62.1 (51.5-80.5) mL/min. The frequency of individuals who underwent at least one peritonitis attack during the follow-up period was 33.3% (n=18). The overall peritonitis rate was 0.1 episodes per year per individual.

The alteration of peritoneal membrane permeability was analyzed. The DPRC parameter was used to define the peritoneal membrane transport rate. The first and last PET results were compared to the calculation of changes in DPRC. High average was the most frequent subgroup, 35% (n=21) in the first PET and 46.7% (n=28) in the last PET. The results are summarized in Table 2.

First, peritoneal permeability alteration was analyzed according to DPRC values. The mean of the first DPRC value was 0.64±0.14, and the mean of the last DPRC value was 0.68±0.11 in all patients. An overall 5.8% increase was observed in the average DPRC value during the follow-up period. However, there was no statistically significant difference between the first and the last DPCR pairs (p=0.103). In addition, there

**Table 1. Demographic features and laboratory results of patients**

| Parameters | Descriptives |
|---|---|
| Gender | |
| Male | 29 (48.3%) |
| Female | 31 (51.7%) |
| Age (years) | 52.9±14.3 |
| BMI ($kg/m^2$) | 26.92±5.32 |
| Grem1 (ng/mL) | 164.9 (81.6-164.9) |
| BUN (mg/dL) | 53.04±12.66 |
| Creatinine (mg/dL) | 8.4±2.8 |
| Uric acid (mg/dL) | 5.5±1.2 |
| Calcium (mg/dL) | 9.0 (8.6-9.6) |
| Phosphorus (mg/dL) | 4.6±1.0 |
| PTH (pg/mL) | 419 (262-565) |
| Sodium (mEq/L) | 137.6±4.5 |
| Potassium (mEq/L) | 4.4 (4.0-4.8) |
| Albumin (g/dL) | 3.87±0.35 |
| Glucose (mg/dL) | 120.1 (92.2-129.2) |
| Hemoglobin (g/dL) | 11.5±1.7 |
| Leukocytes (cell/µL) | 7266±2529 |
| Platelet ($10^3$/µL) | 245.0±70.4 |

Values are expressed as mean ± standard deviation, median ($1^{st}$-$3^{rd}$ quartiles). BUN: Blood urea nitrogen, PTH: Parathyroid hormone, DPRC: Dialysate to plasma ratio for creatinine, BMI: Body mass index

**Table 2. Features of patients according to PET results**

| Parameters | First PET | Last PET |
|---|---|---|
| DPRC | 0.64±0.14 | 0.68±0.11 |
| **Classification** | | |
| High | 10 (16.7) | 7 (11.7) |
| High average | 21 (35.0) | 28 (46.7) |
| Low average | 19 (31.6) | 23 (38.3) |
| Low | 10 (16.7) | 2 (3.3) |

Values are expressed as mean ± standard deviation, median (1st-3rd quartiles). DPRC: Dialysate to plasma ratio for creatinine, PET: Peritoneal equalization test

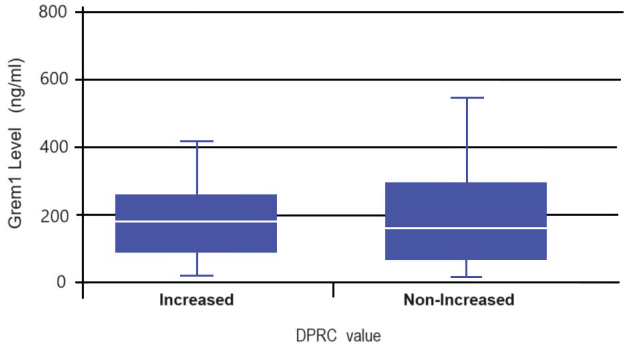


**Figure 1.** Comparison of Grem1 levels according to dialysate to plasma ratio for creatinine alteration status
DPRC: Dialysate to plasma ratio for creatinine

was no statistically significant difference between the increasing DPRC and non-increasing DPRC groups according to Grem1 levels (p=0.783). The results are shown in Figure 1.

Second, peritoneal permeability alteration was analyzed according to PET classification. Stable status was observed in 45% (27) patients, ascending in 31.7% (19) patients, and descending in 23.3% (14) patients. The median plasma Grem1 levels of these groups were as follows: 204.2 ng/mL in stable permeability class patients, 168.2 ng/mL in ascending permeability class patients, and 196.2 ng/mL in descending permeability class patients. In the One-Way ANOVA test, there was no statistically significant difference between the groups in terms of Grem1 levels (p=0.709). The results are shown in Figure 2.

There was no correlation between Grem1 and peritonitis attacks (p=0.256). A statistically significant weak correlation was determined between Grem1 levels and BMI in the Pearson analysis (r=-0.273, p=0.035). However, no statistically significant correlation was identified with important parameters such as the last DPRC (r=0.224, p=0.084), UF volume, Kt/V, and PD duration. The results are illustrated in Figure 3.

## Discussion

In this study, we focused on peritoneal permeability alterations, which are an important problem in PD practice. We investigated a possible relationship between Grem1 and peritoneal permeability; however, we have not identified any association. We chose Grem1 protein in this study because of its antagonistic effect against BMP-7. We considered that

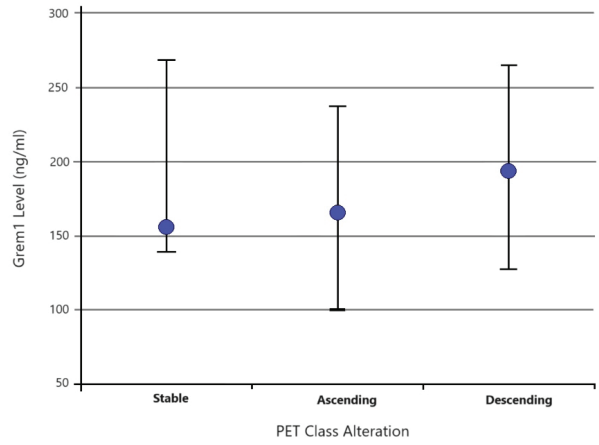


**Figure 2.** Comparison of Grem1 levels according to peritoneal equalization test class changing status
PET: Peritoneal equalization test

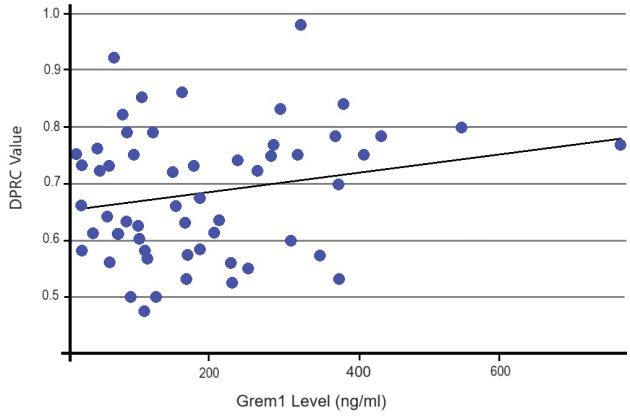


**Figure 3.** Correlation analysis of the last dialysate to plasma ratio for creatinine value and Grem1 levels
DPRC: Dialysate to plasma ratio for creatinine

determining a possible relationship would elucidate the pathogenesis of peritoneal membrane permeability change and may also contribute to treatment options.

In our cohort, we observed an increased average DPRC value (5.8%) during the follow-up period. In addition, increasing peritoneal permeability according to PET classification was observed in 37.1% of the patients at the end of the follow-up. Peritoneal membrane permeability is essential in PD practice. It is among the highest ranks in the factors affecting the performance of dialysis. Membrane permeability should be considered when determining the appropriate solutions and dwell durations for the patients. In addition, adequate clearance of uremic toxins and UF volume are directly affected by membrane permeability (10).

Extracellular signaling molecules such as TGF-β are implicated as drivers of fibrosis-related diseases. In particular, their role in diabetic nephropathy has been well demonstrated. Within these intricate mechanisms, Grem1 is involved as a BMP7 antagonist. In addition,

BMP7 has antagonistic effects against TGF-β and fibrosis (11). As a result, these cytokines and advanced glycation end products play a crucial role in peritoneal membrane fibrosis. Furthermore, long-term PD can lead to peritoneal membrane deterioration, such as increased membrane transport rate (12).

The association between BMP-7 levels in PD effluent fluid and peritoneal transport characteristics has been demonstrated in several studies. The reduction of peritoneal thickness by BMP-7 was shown in animal PD models. Yu et al. (13) also observed that high glucose exposure by dialysate decreased the expression of BMP-7 protein. In a mouse model, Grem1 overexpression in the peritoneum-induced submesothelial thickening, fibrosis, and angiogenesis. In addition, Grem1 was associated with decreased expression of BMP-4 and BMP-7. These effects of Grem1 resulted in EMT in mice (14).

Grem1 levels are increased in renal fibrotic conditions, including acute kidney injury, diabetic nephropathy, chronic allograft nephropathy, and immune glomerulonephritis (3). In particular, its crucial role is well demonstrated in diabetic kidney disease via many studies. A *Grem1* gene variant associated with diabetic nephropathy. Grem1 mRNA levels correlate with serum creatinine levels and tubulointerstitial fibrosis in diabetic nephropathy (15). In the literature review, it was seen that Grem1 has been less investigated on peritoneal permeability. Moreover, we noticed that these were almost all experimental studies and the clinical-based study was not much. Ruiz-Carpio et al. (16) did not determine any association between a high peritoneal transport status and PD effluent Grem1 levels in PD patients. In the aforementioned study, Grem1 was used as a biomarker of the genetic reprograming of EMT. Similarly, a hypothetically expected relationship could not be determined in our study either.

### Study Limitations

Several limitations could have influenced the results of this study. First, we measured Grem1 in PD effluent fluid. This assessment can evaluate the possible relationship. In addition, we did not assess UF failure status in this cohort. Subgroup analysis could be conducted in patients with UF failure. Furthermore, if the initial Grem1 levels of the patients had been measured, the relationship between changes in Grem1 levels relative to the baseline and alterations in peritoneal permeability could have been examined.

## Conclusion

We did not identify any correlation between changes in peritoneal permeability and plasma Grem1 levels. However, we have emphasized the importance of novel biomarkers that could predict changes in peritoneal permeability in this study. Finally, PD clinical practice requires more research on membrane pathophysiology to attain the best clinical outcomes.

**Ethics Committee Approval:** This study was designed as a single-center study. Patients enrolled between 01.01.2020 and 01.01.2021. The study was approved by the Erciyes University Ethics Committee (approval number: 2019/678, date: 09.10.2019).

**Informed Consent:** Written informed consent was obtained from the patients by explaining the procedure of the study.

**Authorship Contributions:** Surgical and Medical Practices - C.U., A.G.; Concept - C.U., A.G., İ.K.; Design - C.U., İ.K.; Data Collection or Processing - A.G., H.Ç.; Analysis or Interpretation - H.Ç.; Literature Search - C.U., H.Ç.; Writing - C.U., İ.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** This project was funded by the Erciyes University Scientific Research Projects Coordination Unit with TSA-2020-9666 number.

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