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## Original Articles



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### Original Articles

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# Impact of the HALP Score on Long-Term Mortality among Patients Undergoing EVAR

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## ABSTRACT

**Introduction:** Endovascular aortic repair (EVAR) is commonly used for abdominal aortic aneurysms, but its mortality rate remains high. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score, which measures hemoglobin, albumin, lymphocyte, and platelet levels, provides prognostic value by reflecting the nutritional status and systemic inflammation. This study aimed to explore the relationship between the HALP score upon admission and long-term mortality in patients with EVAR.

**Methods:** Consecutive patients with EVAR at our tertiary center from October 2010 to August 2021 were retrospectively analyzed. HALP scores were calculated using the following formula: hemoglobin (g/L) × albumin (g/L) × lymphocyte count (/L)/platelet count (/L). In-hospital and long-term mortality data were extracted. Receiver operating characteristic curve analysis identified predictors of in-hospital mortality. Multivariate Cox regression analysis was performed to examine determinants of long-term mortality.

**Results:** Among the 162 participants (mean age: 69.4±8.2 years, 90.1% male), the HALP score was the most significant predictor of in-hospital mortality (area under the curve: 0.752, 95% confidence interval: 0.674-0.830; p<0.001). Multivariate Cox regression analysis revealed HALP (p=0.001) and C-reactive protein (p=0.004) as independent determinants of long-term mortality.

**Conclusion:** This study is the first to investigate the association between the HALP score and in-hospital and long-term mortality in EVAR patients. The HALP score is a robust prognostic tool compared with its components and other parameters in this patient population.

**Keywords:** Endovascular aortic repair, HALP score, long-term mortality

## Introduction

Abdominal aortic aneurysm (AAA) manifests as the enlargement of the abdominal aorta, which is the primary artery in the abdomen. Often asymptomatic, it is typically incidentally diagnosed during imaging examinations. Risk factors associated with AAA include advanced age, male sex, tobacco use, familial predisposition, and atherosclerosis (1-3). AAA, often linked with elevated morbidity and mortality rates if rupture occurs, presents considerable health hazards that necessitate timely detection and suitable intervention. Initially reliant on open surgery, endovascular aneurysm repair (EVAR) emerged in 1986 (4), and it has gained wide acceptance as a safe AAA treatment since Parodi et al.'s (5) report in 1991 (6). Although initially used for elderly or unsuitable surgical candidates, EVAR has become the gold standard for anatomically suitable patients today (7).

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score, a novel indicator reflecting both nutritional status and systemic inflammation, has demonstrated prognostic significance for diverse cancer types (8). Looking at the components that make up HALP; Anemia and hypoalbuminemia signify malnutrition, lymphocytes modulate inflammation, and platelets contribute to thromboembolism and atherosclerosis (9).

Considering advanced age and potential malnutrition in AAA patients undergoing EVAR, alongside atherosclerosis risk factors, we investigated the HALP score's association with long-term mortality in this cohort, recognizing the dearth of similar studies in the literature.

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## Methods

### Study Population

This observational, retrospective study was conducted at a solitary center. We included 162 consecutive patients who underwent successful EVAR between October 2010 and August 2021. All participants were monitored for an average duration of 40±27 months. Patients with AAA rupture, neoplastic diseases, receiving chemotherapy, evidence of acute or chronic inflammatory diseases, glucocorticoid therapy in the last 3 months, immunosuppressive drug use, major trauma or surgery within the last 6 months, severe liver or kidney dysfunction, and those with missing demographic data were excluded. All clinical and demographic data were extracted from the hospital's electronic database. Thirty-nine patients (24.1%) were symptomatic, and the majority (75.9%) were asymptomatic, with AAA diagnosed incidentally through imaging modalities. All procedures were performed in the catheterization laboratory under sterile conditions with anesthesia administered by two experienced invasive cardiologists. Procedural success was determined by the absence of intraoperative fatalities, no need for conversion to open procedures, the absence of type 1-3 endoleaks, peripheral arterial circulation issues, and no stenosis in the renal and hypogastric arteries. After the procedure, all patients underwent postoperative monitoring in the coronary intensive care unit. Blood samples were collected from all patients via the antecubital vein following a 12 h fast prior to the endovascular procedure. Complete blood counts and biochemical analyses were conducted using an automated analyzer (Roche Diagnostic Modular Systems, Tokyo, Japan) at our institution. All patients were monitored for an average duration of 40±27 months. The study's endpoint was long-term all-cause mortality. The study protocol was approved by the University of Health Sciences Turkey, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital's Ethics and Research Committee and adhered to the principles of the Helsinki Declaration (approval number: 2024.01-11, date: 27.02.2024). Written informed consent was obtained from all participants.

### Definition

The HALP score was calculated using the following formula: hemoglobin level (g/L) × albumin level (g/L) × lymphocyte count (/L)/platelet count (/L). The score was determined for each patient. Coronary artery disease included a history of angina pectoris, myocardial infarction, or coronary revascularization. Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis or emphysema. Chronic kidney failure was defined as an estimated glomerular filtration rate ≤60 mL/min. Cerebrovascular accident involving a history of stroke or transient ischemic attack. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dL, hemoglobin A1C ≥6.5%, or prescribed antidiabetic medication. High cholesterol was defined as a lipid-lowering drug use or LDL-C level ≥140 mg/dL. Heart failure was characterized by a preoperative ejection fraction <50%. Peripheral artery disease included arterial disease identified by Doppler ultrasonography and evidenced by lower extremity claudication.

### Follow-up and Outcome

To monitor aortic health, contrast-enhanced computed tomography angiography was performed on all patients at intervals of 1, 6, and 12 months postoperatively, followed by annual evaluations. The study's primary endpoint was all-cause mortality, and patients were monitored from the day of EVAR until death. The reasons and time of mortality were obtained from hospital records and national death registries.

### Statistical Analysis

The normality of variables was evaluated utilizing Kolmogorov-Smirnov tests, histograms, and probability plots. Numeric variables are reported as mean ± standard deviation (e.g., age, AAA diameter, etc.) or median (interquartile range) (e.g., HALP score, triglycerides, etc.) depending on their distribution. Categorical variables like gender, smoking status, etc., are expressed as percentages (%). Numerical variables between the two groups were compared using either unpaired Student's t-test or Mann-Whitney U test, while categorical variables were compared using the chi-square or Fisher's exact test. Kaplan-Meier modeling was utilized to depict the duration until the cessation of service events, serving as a proxy for mortality following aneurysm surgery. The analysis was conducted using SPSS 26.0 software (SPSS, Chicago, IL). Statistical comparisons of the time-to-event data for various interventions and controls were performed using log-rank tests and reported as median survival rates [years ± 95% confidence interval (CI)]. Additionally, in patients undergoing EVAR, a single-variable Cox proportional hazards model was utilized to compute hazard ratios and corresponding 95% CIs for long-term mortality. Multivariable Cox proportional hazards regression models were used to assess potential independent predictors of survival. The significance level was set at $p<0.050$.

## Results

The study comprised 162 participants, with a mean age of 69.4±8.2 years, predominantly consisting of males (146 participants, 90.1%). Throughout the follow-up period, 50 out of 162 participants experienced mortality. Participants were stratified into two cohorts: survivors and non-survivors. The basic demographic, laboratory, and procedural data of the study group are summarized in Table 1. While demographic characteristics were similar between the two groups, non-survivors exhibited higher rates of congestive heart failure ($p=0.013$), COPD ($p=0.021$), and ES replacement requirement ($p<0.001$), whereas survivors demonstrated higher left ventricular ejection fraction (LVEF), % ($p<0.001$).

Regarding laboratory parameters, higher hemoglobin ($p<0.001$), albumin ($p<0.001$), lymphocyte count ($p<0.001$), and HALP score ($p<0.001$) were observed in the survivor group, whereas C-reactive protein (CRP) ($p=0.004$) and glucose ($p=0.023$) values were elevated in the non-survivor group. Other laboratory parameters did not differ significantly between the two groups. No significant differences were found in procedural data between the groups.

Univariate Cox regression analyses were performed to identify determinants of long-term mortality, revealing parameters significantly associated with mortality, such as COPD, LVEF, HALP, Glucose, and CRP (Table 2). In the multivariate Cox regression analysis, HALP ($p=0.001$)

**Table 1. Characteristics of all-cause mortality and survivors among patients undergoing EVAR**

| | All patients (n=162) | Survivors (n=112) | Non-survivors (n=50) | p-value |
|---|---|---|---|---|
| Age, years | 69.4±8.2 | 69±8.2 | 70.3±8.3 | 0.346 |
| Sex (male), n (%) | 146 (90.1) | 100 (89.3) | 46 (92) | 0.593 |
| BMI, kg/m$^2$ | 26.1±3.4 | 25.7±3.1 | 26.9±3.9 | 0.052 |
| Smoking frequency, n (%) | 50 (30.9) | 35 (31.3) | 15 (30) | 0.874 |
| **Comorbidities** | | | | |
| Diabetes mellitus, n (%) | 42 (25.9) | 27 (24.1) | 15 (30) | 0.429 |
| Hypertension, n (%) | 98 (60.5) | 67 (59.8) | 31 (62) | 0.793 |
| CAD, n (%) | 78 (48.1) | 54 (48.2) | 24 (48) | 0.980 |
| CHF, n (%) | 25 (15.4) | 12 (10.7) | 13 (26) | **0.013** |
| Hyperlipidemia, n (%) | 49 (30.2) | 33 (29.5) | 16 (32) | 0.746 |
| History of cancer, n (%) | 14 (8.6) | 12 (10.7) | 2 (4) | 0.160 |
| Cerebrovascular disease, n (%) | 7 (4.3) | 6 (5.4) | 1 (2) | 0.332 |
| Atrial fibrillation, n (%) | 17 (10.5) | 13 (11.6) | 4 (8) | 0.489 |
| PAD, n (%) | 12 (7.4) | 7 (6.3) | 5 (10) | 0.400 |
| COPD, n (%) | 26 (16) | 13 (11.6) | 13 (26) | **0.021** |
| CKD, n (%) | 22 (13.6) | 15 (13.4) | 7 (14) | 0.917 |
| LVEF, (%) | 55.3±9.3 | 57.2±7.8 | 51±10.9 | **<0.001** |
| **Laboratory data** | | | | |
| Hemoglobin, g/dL | 12.6±1.9 | 13±1.8 | 11.8±2 | <0.001 |
| WBC, 10$^6$/L | 7.9±2.4 | 8.1±2.2 | 7.7±2.7 | 0.313 |
| Platelet, 10$^3$/mL | 226.7±77.2 | 226.8±80.9 | 226.4±68.7 | 0.972 |
| Neutrophil, 10$^3$/mL | 4.8±1.9 | 4.7±1.6 | 5±2.5 | 0.315 |
| Lymphocyte, 10$^3$/mL | 2.1±0.8 | 2.2±0.8 | 1.7±0.6 | **<0.001** |
| Albumin, g/dL | 3.9±0.5 | 4±0.4 | 3.7±0.5 | **<0.001** |
| Glucose, mg/dL | 106.4±27.7 | 103.1±25.6 | 113.9±31.1 | **0.023** |
| Creatinine, mg/dL | 1.1±0.4 | 1.1±0.5 | 1.1±0.4 | 0.221 |
| C-reactive protein level, mg/dL | 9 (4-18) | 7 (3-13.8) | 13 (7-33.5) | **0.004** |
| LDL-C, mg/dL | 108.6±37.4 | 104.6±37.6 | 117.7±35.7 | 0.059 |
| HDL-C, mg/dL | 42.8±11.5 | 45.5±12 | 41.3±10.3 | 0.290 |
| Triglyceride, mg/dL | 122 (88-169) | 118 (88.5-160) | 124 (84-185.8) | 0.490 |
| Total cholesterol level, mg/dL | 178±36.7 | 174.7±36.6 | 185.5±36.1 | 0.084 |
| HALP score | 0.45 (0.31-0.64) | 0.52(0.38-0.70) | 0.32(0.24-0.45) | **<0.001** |
| AAA diameter, mm | 65.9±11.6 | 64.9±11.3 | 68.1±12 | 0.102 |
| ES replasmanı, n (%) | 61 (37.7) | 30 (26.8) | 31 (62) | **<0.001** |
| Symptomatic, n (%) | 39 (24.1) | 30 (26.8) | 9 (18) | 0.227 |
| **Procedure-related data** | | | | |
| The type of endograft | | | | 0.311 |
| Medtronic endurant, n (%) | 124 (76.5) | 89 (79.5) | 35 (70) | |
| Triventricular ovation, n (%) | 15 (9.3) | 7 (6.3) | 8 (16) | |
| Cook zenith, n (%) | 9 (5.6) | 7 (6.3) | 2 (4) | |
| Medtronic talent, n (%) | 9 (5.6) | 5 (4.5) | 4 (8) | |
| Vascutec anaconda, n (%) | 3 (1.9) | 2 (1.8) | 1 (2) | |
| Gore exluder, n (%) | 2 (1.2) | 2 (1.8) | 0 (0) | |
| Operation time (min) | 147.8±54.2 | 142.8±60.6 | 158.9±34.1 | 0.080 |
| Scopy time (min) | 31±16.5 | 29.5±17.4 | 34.5±13.7 | 0.070 |
| Fallow time, months | 40±27 | 42.4±27.2 | 34.7±26.1 | 0.094 |

Data are presented as percentage, mean standard deviation, or median (interquartile range). AAA: Abdominal aortic aneurysm, BMI: Body mass index, CAD: Coronary artery bypass disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, HALB: Hemoglobin, albumin, lymphocyte, and platelet, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, PAD: Peripheral artery disease, WBC: White blood cells, min.: Minimum

**Table 2. Univariate and multivariate Cox regression analyses to identify long-term predictors of mortality**

| | Univariate analyses | | | Multivariate analyses | | |
|---|---|---|---|---|---|---|
| **Variables** | **HR** | **95% CI (lower-upper)** | **p-value** | **HR** | **95% CI (lower-upper)** | **p-value** |
| COPD | 2.234 | 1.182-4.220 | **0.013** | 1.461 | 0.584-3.652 | 0.417 |
| LVEF | 0.965 | 0.942-0.988 | **0.003** | 0.974 | 0.942-1.007 | 0.118 |
| HALP | 0.223 | 0.108-0.459 | **<0.001** | 0.229 | 0.093-0.565 | **0.001** |
| Glukoz | 1.009 | 1.001-1.018 | **0.034** | 1.009 | 0.999-1.018 | 0.075 |
| CRP | 1.015 | 1.008-1.022 | **<0.001** | 1.012 | 1.004-1.020 | **0.004** |

HR: Hazard ratio, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, HALB: Hemoglobin, albumin, lymphocyte, and platelet, CRP: C-reactive protein

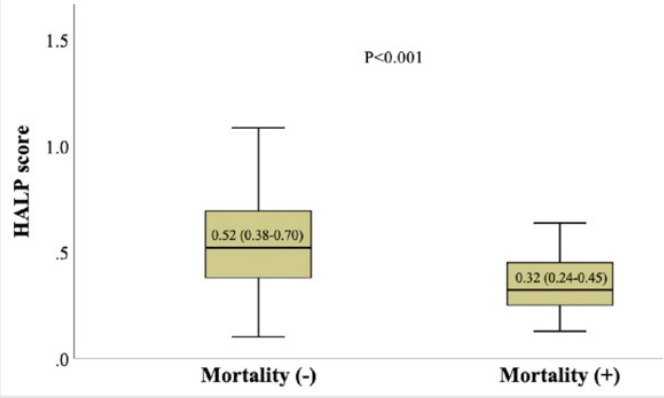
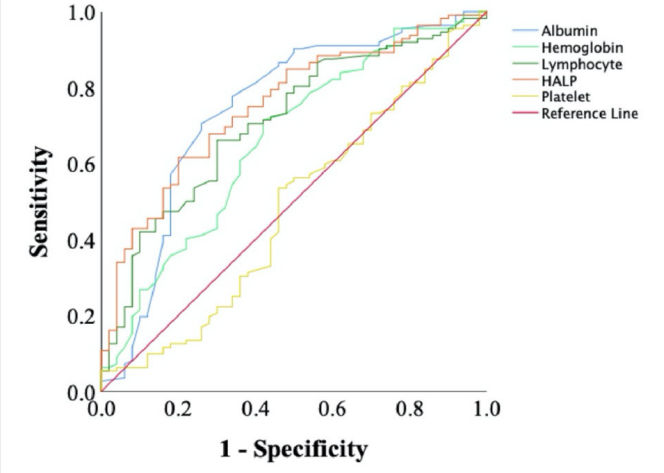



**Figure 1.** Box plots comparing HALP scores between patients with and without mortality
HALB: Hemoglobin, albumin, lymphocyte, and platelet




| | AUC | 95%CI Lower-Upper | P value |
|---|---|---|---|
| Albumin | 742 | 0.652-0.833 | **<0.001** |
| Hemoglobin | 660 | 0.567-0.752 | **0.001** |
| Lymphocyte | 710 | 0.625-0.794 | **<0.001** |
| HALP | 752 | 0.674-0.830 | **<0.001** |
| Platelet | 480 | 0.380-0.580 | 0.679 |

**Figure 2.** ROC curve analysis including albumin, hemoglobin, lenfosit, HALP, and platelet values was performed to determine the most suitable parameter for predicting long-term mortality
ROC: Receiver operating characteristic

and CRP (p=0.004) emerged as independent determinants of long-term mortality.

To identify the most suitable parameter indicating in-hospital mortality, a receiver operating characteristic curve analysis was conducted using albumin, hemoglobin, lymphocyte, platelet, and the combined HALP score. The HALP score exhibited the highest predictive power, with an area under the curve of 0.752 (95% CI: 0.674-0.830; p<0.001). A cut-off value of 0.46 for the HALP score was used to detect long-term mortality development with a sensitivity of 61.6% and specificity of 80%.

Kaplan-Meier survival analysis illustrated that patients with higher HALP scores experienced significantly increased long-term mortality rates (log-rank: p<0.001).

## Discussion

Our study, to our knowledge, represents the first investigation into the use of the HALP score in evaluating prognosis in this patient cohort. The primary findings of our study are as follows:

1. The HALP score is an independent predictor of long-term mortality among patients undergoing EVAR.

2. The HALP score is the strongest parameter indicating in-hospital mortality compared with its components, including hemoglobin, albumin, lymphocytes, and platelets.

3. Patients' survival time is prolonged as the HALP score increases.

As life expectancy increases, the risk of AAA also rises (1), and with the assistance of advancing technology, AAA can be detected early and treated. The advent of cutting-edge percutaneous suture-mediated vascular closure devices and the development of lower-profile endograft devices have revolutionized the aortic repair landscape. These advancements have rendered complete percutaneous endovascular access not only a viable but also an unequivocally preferable option for patients undergoing aortic repair procedures (10). With the increasing number of patients undergoing EVAR in this field and their impact on in-hospital and long-term mortalities in the postoperative period, it has become a matter of curiosity whether the HALP score, which has been previously proven to affect prognosis in cancer and stroke patients, would provide any benefit in this patient group (8,11).

In a study by Diehm et al. (12), the relationship between hemoglobin, one of the parameters constituting the HALP score, AAA diameter, and long-term survival in patients undergoing EVAR was investigated, and

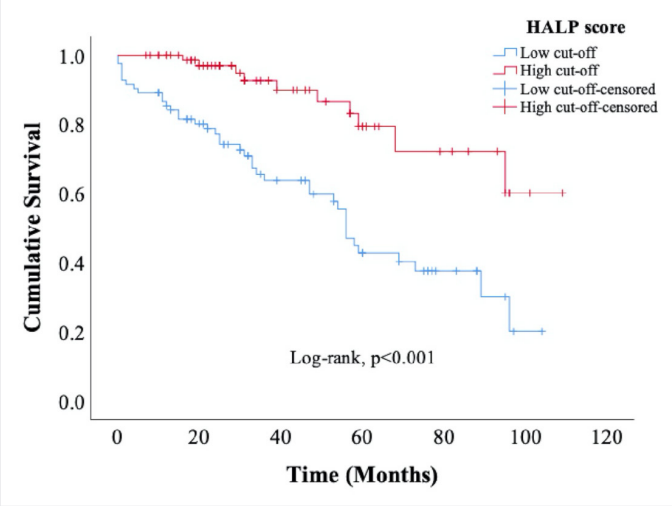



**Figure 3.** Kaplan-Meier survival curves of the HALP score in long-term mortality
HALP: Hemoglobin, albumin, lymphocyte, and platelet

during long-term follow-up, survival was significantly lower in patients with anemia than in those without anemia. Moreover, in a separate investigation by Nishibe et al. (13), the association between albumin, another component of the HALP score, and long-term mortality among patients undergoing EVAR was explored. Their findings revealed that albumin was an independent risk factor for long-term mortality in this patient population undergoing EVAR. Additionally, the relationship between the Geriatric Nutritional Risk Index, which is used as a marker of malnutrition, and long-term mortality in patients undergoing EVAR has been demonstrated in other studies (13,14). The difference between these studies and ours lies in the evaluation of albumin and body mass index. However, systemic inflammation plays an undeniable role in the formation of AAA and the post-EVAR treatment process.

The relationship between AAA and inflammatory processes is an undisputed fact. CRP is recognized as an acute-phase protein that is typically elevated in patients with AAA. In a study conducted by Shangwei et al. (15), it was determined that elevated serum high-sensitivity C-reactive protein (hsCRP) levels constituted an independent risk factor for AAA after adjusting for confounding variables through adjustment. In a separate investigation conducted by Wang et al. (16), the correlation between hsCRP levels and the presence of AAA was examined. Their findings suggested that hsCRP levels could serve as a diagnostic biomarker in AAA patients with medium or small aortic diameters, but not in those with large aortic diameters (16). In this study, we observed that preoperative CRP levels independently contributed to long-term mortality after EVAR, together with the HALP score.

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are recognized as biomarkers of systemic inflammation and atherosclerosis stemming from distinct immune pathways (17-19). In a study by King et al. (20), an increase in preoperative NLR was associated with increased mortality after EVAR. Octeau et al. (21) showed in another study that a high NLR was significantly associated with post-EVAR mortality and reintervention, even after adjusting for variables such as age, AAA diameter, and NLR-related clinical comorbidities. Furthermore, the indirect relationship between NLR and PLR and aneurysm sac shrinkage, which is considered an indicator of postoperative improvement, appears to be connected to inflammation (21). Patients with lower preoperative inflammatory status are more likely to have aneurysm sac regression after EVAR, leading to higher medium- and long-term survival rates (22). As demonstrated in these studies, systemic inflammation clearly affects long-term mortality. In this study, we evaluated the relationship between the HALP score and long-term mortality among patients undergoing EVAR, reflecting both nutritional status and systemic inflammation. In this regard, our study appears to be more comprehensive and complementary than other studies.

The HALP score is a simple index that can be easily calculated from routine complete blood counts at hospital admission without any additional cost or additional work. The ease of calculating the HALP score at bedside is advantageous compared with other indices. This risk stratification approach could empower clinicians to identify patients at elevated risk and tailor their treatment, incorporating intensive medical therapy and implementing vigilant monitoring protocols for such individuals. However, further prospective studies involving long-term follow-up in a larger multicenter patient population are needed to elucidate the effectiveness of the HALP score in predicting in-hospital and out-of-hospital morbidity and mortality in treated patients with EVAR.

### Study Limitations

The study's single-center and retrospective nature can impact the generalizability of the findings. Future multicenter, prospective studies may provide more comprehensive insights. The relatively small sample size in this study is a significant limitation. Larger prospective cohort studies are essential to validate and extend the current findings. Second, patients with AAA who were medically observed and surgically repaired were not included in the study, which may have caused this score to not be generalizable to other patient groups. Incorporating this aspect into future studies may provide a more holistic understanding of patients' conditions. Finally, the HALP score was not compared with other risk scoring systems linked to mortality in patients undergoing EVAR.

## Conclusion

In our study, we used the HALP score, which has not been previously evaluated in this patient group, and found that the HALP score is an independent predictor of long-term mortality in patients undergoing EVAR. This result provides us with a new perspective that the HALP score, which can be easily calculated and applied in practice, can be used as a guide in the follow-up and treatment of EVAR patients.

**Ethics Committee Approval:** The study protocol was approved by the University of Health Sciences Turkey, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital's Ethics and Research Committee and adhered to the principles of the Helsinki Declaration (approval number: 2024.01-11, date: 27.02.2024).

**Informed Consent:** Written informed consent was obtained from all participants.

**Authorship Contributions:** Surgical and Medical Practices - M.A., Ö.Ç., Concept - M.A., A.A.Ş., Design - M.A., M.K., N.U., A.A.Ş., Data Collection or Processing - M.A., T.A., O.E., S.A., Analysis or Interpretation - M.A., A.E., Y.D., Literature Search - M.A., A.E., Y.D., Writing - M.A., A.E.,

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

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## References

1. Singh K, Bønaa KH, Jacobsen BK, Bjørk L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: The Tromsø Study. Am J Epidemiol. 2001; 154: 236-44.
2. Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, et al. Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. Ann Intern Med. 1997; 126: 441-9.
3. Vardulaki KA, Walker NM, Day NE, Duffy SW, Ashton HA, Scott RA. Quantifying the risks of hypertension, age, sex and smoking in patients with abdominal aortic aneurysm. Br J Surg. 2000; 87: 195-200.
4. Volodos' NL, Shekhanin VE, Karpovich IP, Troian VI, Gur'ev IuA. A self-fixing synthetic blood vessel endoprosthesis. Vestn Khir Im I I Grek. 1986; 137: 123-5.
5. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg. 1991; 5: 491-9.
6. Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm. Cochrane Database Syst Rev. 2014; 2014: CD004178.
7. Chaikof EL, Dalman RL, Eskandar MK, Jackson BM, Lee WA, Mansour MA, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018; 67: 2-77.
8. Tian M, Li Y, Wang X, Tian X, Pei L-lu, Wang X, et al. The hemoglobin, albumin, lymphocyte, and platelet (halp) score is associated with poor outcome of acute ischemic stroke. Front Neurol. 2021; 11: 610318.
9. Reininger AJ, Bernlochner I, Penz SM, Ravanat C, Smethurst P, Farndale RW, et al. A 2-step mechanism of arterial thrombus formation induced by human atherosclerotic plaques. J Am Coll Cardiol. 2010; 55: 1147-58.
10. Walker TG, Kalva SP, Yeddula K, Wicky S, Kundu S, Drescher, et al. Clinical practice guidelines for endovascular abdominal aortic aneurysm repair: written by the Standards of Practice Committee for the Society of Interventional Radiology and endorsed by the Cardiovascular and Interventional Radiological Society of Europe and the Canadian Interventional Radiology Association. J Vasc Interv Radiol. 2010; 21: 1632-55.
11. Guo Y, Shi D, Zhang J, Mao S, Wang L, Zhang W, Zhang Z, Jin L, Yang B, Ye L, Yao X. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a novel significant prognostic factor for patients with metastatic prostate cancer undergoing cytoreductive radical prostatectomy. J Cancer. 2019; 10: 81-91.
12. Diehm N, Benenati JF, Becker GJ, Quesada R, Tsoukas AI, Katzen BT, et al. Anemia is associated with abdominal aortic aneurysm (AAA) size and decreased long-term survival after endovascular AAA repair. J Vasc Surg. 2007; 46: 676-81.
13. Nishibe T, Kano M, Matsumoto R, Ogino H, Koizumi J, Dardik A. Prognostic value of nutritional markers for long-term mortality in patients undergoing endovascular aortic repair. Ann Vasc Dis. 2023; 16: 124-30.
14. Shuta I, Akio K, Yohei K, Tsuruoka T, Sugimoto M, Niimi K, et al. Preoperative sarcopenia and malnutrition are correlated with poor long-term survival after endovascular abdominal aortic aneurysm repair. Surg Today. 2022; 52: 98-105.
15. Shangwei Z, Yingqi W, Jiang X, Zhongyin W, Juan J, Dafang C, et al. Serum high-sensitive C-reactive protein level and CRP genetic polymorphisms are associated with abdominal aortic aneurysm. Ann Vasc Surg. 2017; 45: 186-92.
16. Wang Y, Shen G, Wang H, Yao Y, Sun Q, Jing B, et al. Association of high sensitivity C-reactive protein and abdominal aortic aneurysm: a meta-analysis and systematic review. Curr Med Res Opin. 2017; 33: 2145-52.
17. Azab B, Camacho-Rivera M, Taioli E. Average values and racial differences of neutrophil lymphocyte ratio among a nationally representative sample of United States subjects. PLoS One. 2014; 9: e112361.
18. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013; 11: 55-9.
19. Jackson SM, Perry LA, Borg C, Ramson DM, Campbell R, Liu Z, et al. Prognostic importance of preoperative neutrophil-lymphocyte ratio in vascular surgery: systematic review and meta-analysis. Vasc Endovasc Surg. 2020; 54: 697-706.
20. King AH, Schmaier AH, Harth KC, Kumins NH, Wong VL, Zidar DA, et al. Elevated neutrophil-lymphocyte ratio predicts mortality following elective endovascular aneurysm repair. J Vasc Surg. 2020; 72: 129-37.
21. Octeau D, Faries C, Barnes H, Nakazawa KR, Rao AJ, Ting W, et al. Neutrophil-to-lymphocyte ratio associated with adverse events after endovascular aneurysm repair (EVAR). Ann Vasc Surg. 2021: 75: 45-54.
22. Pasqui E, Donato G, Molina C, Abu Leil M, Anzaldi MG, Galzerano G, et al. Residual aneurysmal sac shrinkage post-endovascular aneurysm repair: the role of preoperative inflammatory markers. Biomedicines. 2023; 11: 1920.

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# Efficacy and Tolerability of First-Line Anti-eGFR and Anti-VEGF Therapy in Elderly Patients with Ras-Wild Metastatic Colon Cancer

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## ABSTRACT

**Introduction:** Adding targeted agents to chemotherapy for metastatic colorectal cancer increases survival. There have been no clinical trials in older populations comparing the efficacy of the targeted agents. We aimed to compare the efficacy and tolerability of anti-epidermal growth factor receptor (anti-eGFR) and anti-vascular endotelial growth factor (anti-VEGF) in elderly patients with metastatic colorectal cancer in the first-line setting.

**Methods:** A total of 89 elderly patients diagnosed with KRAS wild metastatic colorectal cancer who received anti-eGFR or anti-VEGF therapy in the first-line setting were included in the study. Patients received anti-eGFR plus chemotherapy compared with anti-VEGF plus chemotherapy according to general characteristics, response rates, progression-free and overall survival (OS), and non-hematological toxicities.

**Results:** The median age was 70 (65-81) years old in anti-eGFR group and 69 (65-78) in anti-VEGF group in our study. The progression-free survival was 11 months in the anti-eGFR group and 10 months in anti-VEGF group (p=0.053). OS was not reached at the median of 28 months in the anti-eGFR group and there were no statistically difference (p=0.77).

**Conclusion:** Progression-free and OS rates were similar between the anti-eGFR and anti-VEGF groups in older patients with metastatic colorectal cancer. Grade 3-4 rash is the most common adverse event in the anti-eGFR group. Pulmoner thromboembolism and diarrhea are the most common adverse events in the anti-VEGF group. Old age is not a barrier for use biological agents.

**Keywords:** Colon cancer, vascular endotelial growth factor, epidermal growth factor, elderly

## Introduction

Colon cancer is mostly diagnosed in older people. Nearly 70% of patients diagnosed with colon cancer are over 65 years of age (1). Comorbidities are more common in older patients than in younger individuals (2). The most appropriate therapy for elderly patients diagnosed with metastatic colorectal cancer is not clear because these age group is small among the studies (3).

Cetuximab and panitumumab are monoclonal antibodies that target the epidermal-growth factor receptor (e-GFR) (4,5). Bevacizumab is a monoclonal antibody that targets vascular endotelial growth factor (VEGF) (6). Previous studies have shown that chemotherapy combined with targeted agents confers a survival benefit compared with chemotherapy alone in older populations (7-9). There have been no clinical trials in older populations comparing the efficacy of the targeted agents. Some previous studies have shown that progression-free survival (PFS) benefit was similar between the older and younger groups (10). However, these targeted agents cause some toxicities like cutaneous reactions and thromboembolic events (11). These adverse reactions sometimes cause treatment discontinuation. Because the elderly patients were mostly frail.

We aimed to compare the efficacy and tolerability of anti-eGFR and anti-VEGF in elderly patients with metastatic colorectal cancer in the first-line setting.

## Methods

Patients aged 65 or older who were diagnosed with KRAS wild metastatic colorectal cancer and received first-line chemotherapy combined with anti-eGFR or anti-VEGF therapy in Kayseri City Training and Research Hospital and Erciyes University Faculty of Medicine over the last 15 years were retrospectively reviewed and included in the study. Patients who received therapy for less than 2 months were excluded.

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Data collected from the hospital's patient records included patient characteristics, chemotherapy regimens administered, chemotherapy responses, metastatic sites, number of metastatic sites, and date of death.

Patients received anti-eGFR plus chemotherapy compared with anti-VEGF plus chemotherapy according to general characteristics, response rates, progression-free and overall survival (OS), and non-hematological toxicities.

The present study was approved by the Ethics Committee of Kayseri City Training and Research Hospital (approval number: 758, date: 20.12.2022).

### Statistical Analysis

Median, minimum, maximum, and frequencies were defined. The Kaplan-Meier method and log-rank test were used to analyze PFS. PFS was defined as the date from the first targeted therapy combined with chemotherapy until progression or death. OS was defined as the time of chemotherapy and the initiation of targeted agents to the date of death or last known contact. A p-value <0.05 was considered statistically significant. Response was evaluated as complete response (CR), partial response (PR), stable disease (SD), or progressive disease. The Statistical Package for Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA) software was used in all statistical analyses.

## Results

### Patients and Characteristics

A total of 89 patients diagnosed with KRAS wild metastatic colorectal cancer and who received anti-eGFR or anti-VEGF in the first-line setting were included in the study. Sixty-two (70%) patients were in the anti-eGFR group and 27 (30%) were in the anti-VEGF group.

The median ages were 70 (65-81) years in the anti-eGFR group and 69 (65-78) in the anti-VEGF group in our study. Twenty-two of them (35%) were female, and 40 (65%) were male in the anti-eGFR group. Sixteen of the participants (59%) were female, and 11 (41%) were male in the anti-VEGF group. The primary tumor was right sided in 9 patients (15%) in the anti-eGFR group and in 7 (26%) patients in the VEGF group. All characteristics are shown in Table 1.

### Response and Survival

In the anti-eGFR group, an overall response rate was achieved in 53 patients (86%). Three patients had CR (5%), 36 had PR (58%), and 14 (23%) had SD.

In the VEGF group, an overall response rate was achieved in 26 patients (96%). There was no CR. Fifteen patients had PR (55%), 11 patients (41%) had a SD.

The PFS was 11 (5.44-16.55) months in the anti-eGFR group and 10 (9.18-10.82) months in the anti-VEGF group. There were no significant difference (p=0.053). OS was not reached at the median in anti-eGFR group, 28 (22.47-33.52) months in anti-VEGF group and there were no statistically significant differences (p=0.77) (Figure 1).

### Toxicity

The most common non-hematological adverse events were rash (18%) and thromboembolism (with 5%) in the anti-eGFR group. Pulmoner thromboembolism is the most common adverse event with 4% in anti-VEGF group (Table 1).

## Discussion

In this study, we compared anti-eGFR plus chemotherapy and anti-VEGF plus chemotherapy according to efficacy and tolerability in elderly metastatic KRAS wild metastatic colorectal cancer. We found no

**Table 1. General characteristics**

| Characteristics | Anti-eGFR n, (%) (n=62; 70%) | Anti-VEGF n, (%) (n=27; 30%) |
|---|---|---|
| Age (years; median; minimum-maximum) | 70 (65-81) | 69 (65-78) |
| **Gender** | | |
| Female | 22 (35) | 16 (59) |
| Male | 40 (65) | 11 (41) |
| **Initially metastatic** | | |
| Yes | 50 (80) | 18 (67) |
| No | 12 (20) | 9 (33) |
| **Neo/adjuvant chemotherapy** | | |
| Yes | 10 (20) | 7 (26) |
| No | 52 (80) | 20 (74) |
| **Tumors site** | | |
| Right colon | 9 (15) | 7 (26) |
| Left colon | 53 (85) | 20 (74) |
| **Chemotherapy combination** | | |
| Irinotecan based | 28 (45) | 10 (37) |
| Oxaliplatin based | 34 (55) | 17 (63) |
| **Metastatic site** | | |
| Liver | 45 (73) | 19 (70) |
| Lung | 23 (37) | 8 (30) |
| Peritoneum | 6 (10) | 5 (19) |
| Non-regional lymph nodes | 14 (23) | 7 (26) |
| **Number of metastatic sites** | | |
| 1 region | 38 (61) | 15 (56) |
| ≥2 region | 24 (39) | 12 (44) |
| **Treatment response** | | |
| Complete response | 3 (5) | 0 (0) |
| Partial response | 36 (58) | 15 (55) |
| Stable disease | 14 (23) | 11 (41) |
| Progressive disease | 9 (14) | 1 (4) |
| **Grade 3-4 toxicity** | | |
| Rash | 11 (18) | 0 |
| Pulmoner thromboembolism | 3 (5) | 1 (4) |
| Diarrhea | 1 (2) | 1 (4) |
| Unavailable | 15 (24) | 5 (19) |

eGFR: Epidermal growth factor receptor, VEGF: Vascular endotelial growth factor

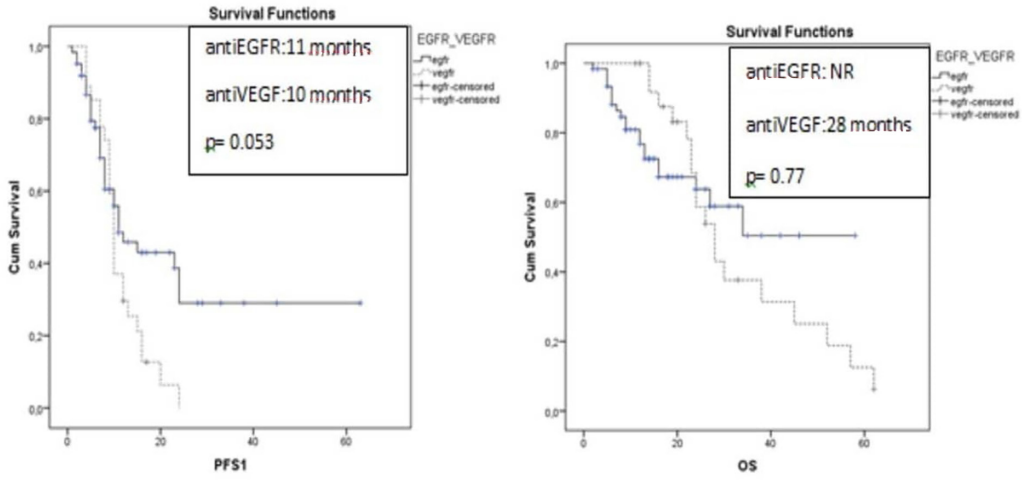


**Figure 1.** Progression free and overall survival
eGFR: Epidermal growth factor receptor, VEGF: Vascular endotelial growth factor

significant differences in PFS and OS between the anti-eGFR and anti-VEGF groups. Grade 3-4 toxicities were observed mostly in the rash in the anti-eGFR group, pulmoner embolism in the bevacizumab group, and diarrhea in the anti-VEGF group. Rash was more common in the anti-eGFR group than anti-VEGF group. Pulmoner thromboembolism was similar between the anti-eGFR and anti-VEGF group.

Treatment of older patients with metastatic colorectal cancer remains controversial. Recent studies suggest that treatment toxicitis is more common in elderly individuals, and these individuals are more likely to discontinue treatment (12). The efficacy of chemotherapy is similar in elderly and younger adults (13). The survival of patients who receive chemotherapy combined with biological agents is higher among older patients (7-9).

In our study, we found that the PFS was statistically similar between the anti-eGFR and anti-VEGF groups. In the CALGB/SWOG 80405 study, chemotherapy and cetuximab compared chemotherapy and bevacizumab. They found no significant differences between the PFS and OS. The median PFS was 10.5 months in chemotherapy-cetuximab group and 10.6 months chemotherapy-bevacizumab group (p=0.45). Although our study population comprised elderly individuals, our PFS results were similar to these results. OS was 30 months in the cetuximab and 29 months in the bevacizumab groups in the CALGB/SWOG 80405 study (14). In our study, the median OS was not reached at the median point of 28 months in the anti-eGFR group and the anti-VEGF group. In the CALGB study, the median age was 59. They did not compare survival in older people. The PEAK study compared chemotherapy and panitumumab with chemotherapy and bevacizumab (15). They observed no significant differences between the PFS and OS groups. In this study, the median age was 62 in panitumumab group, sixty in bevacizumab group. In a pooled analyses of four studies, they found 9.3 months for PFS and 17.9 months in patients older than 65 years with metastatic colorectal cancer who received chemotherapy and bevacizumab (10). In this study, in the bevacizumab group, the patients' median age was higher than ours. The median age was 72 years. Perhaps the higher median age in this study was the reason for the survival difference between them and ours.

In the CALGB study, arterial thrombotic events were not observed higher than 5% in both cetuximab and bevacizumab groups (14). In the PEAK study in panitumumab group grade 3-4 rash was observed in 15% of patients in the panitumumab group and 0% in the bevacizumab group. Deep vein thrombosis was observed in 2% of patients in the panitumumab group and 8% in the bevacizumab group (15). Arterial thromboembolic events were observed in 5.7% of older patients who received bevacizumab (10). In this study, there was no greater difference in non-hematological adverse events between younger and older patients (10). We observed rash in our study in 18% of the patients and pulmoner thromboembolism in 5% of the anti-eGFR group. Pulmoner thromboembolism was 4% in anti-VEGF group in our study.

### Study Limitations

This study has several limitations. First, the number of patients was small. Second, we could not identify adverse events in some patients. We only analyzed available toxicities. Third, we could not perform all mutation analyses in our patients due to the retrospective nature of the study. The results that expand RAS, BRAF, and other mutations are valuable. The retrospective nature and small sample size are some of the limitations of our study.

## Conclusion

Progression-free and OS rates were similar between the anti-eGFR and anti-VEGF groups in older patients with metastatic colorectal cancer. Grade 3-4 rash is the most common adverse event in the anti-eGFR group. Pulmoner thromboembolism is the most common adverse event in the anti-VEGF group. Old age is not a barrier for use biological agents.

**Ethics Committee Approval:** The present study was approved by the Ethics Committee of Kayseri City Training and Research Hospital (approval number: 758, date: 20.12.2022).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Concept - E.D., S.T.F., M.E., O.B., M.İ., M.Ö.; Design - E.D., S.T.F., O.B., M.İ., M.Ö.; Data Collection or Processing - E.D.,

S.T.F., M.E.; Analysis or Interpretation - E.D., O.B., M.İ., M.Ö.; Literature Search - E.D., S.T.F., M.E., O.B., M.İ., M.Ö.; Writing - E.D.

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## References

1. National Cancer Institute. SEER cancer statictics. review 1975-2001. Available at:http://seer.cancer.gov/csr/1975-2001
2. González-Senac NM, Mayordomo-Cava J, Macías-Valle A, Aldama-Marín P, Majuelos González S, Cruz Arnés ML et al. Colorectal cancer in elderly patients with surgical indication: state of the art, current management, role of frailty and benefits of a geriatric liaison. Int J Environ Res Public Health. 2021; 18: 6072.
3. Sastre J, Aranda E, Grávalos C, Massutí B, Varella-Garcia M, Rivera F, et al. First-line single-agent cetuximab in elderly patients with metastatic colorectal cancer. A phase II clinical and molecular study of the Spanish group for digestive tumor therapy (TTD). Crit Rev Oncol Hematol. 2011; 77: 78-84.
4. Goldstein NI, Prewett M, Zuklys K, Rockwell P, Mendelsohn J. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. Clin Cancer Res. 1995; 1: 1311-8.
5. Pietrantonio F, Cremolini C, Aprile G, Lonardi S, Orlandi A, Mennitto A, et al. Single-agent panitumumab in frail elderly patients with advanced RAS and BRAF wild-type colorectal cancer: challenging drug label to light up new hope. Oncologist. 2015; 20: 1261-5.
6. Rosen LS. VEGF-targeted therapy: therapeutic potential and recent advances. Oncologist. 2005; 10: 382-91.
7. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol. 2015;26:463-76.
8. Lonardi S, Schirripa M, Buggin F, Antonuzzo L, Merelli B, Boscolo G, et al. First-line FOLFOX plus panitumumab versus 5FU plus panitumumab in RAS-BRAF wild type metastatis colorectal cancer elderly patients: The PANDA study. J Clin Oncol. 2020; 38: 4002.
9. Aparicio T, Bouché O, Taieb J, Maillard E, Kirscher S, Etienne PL, et al. Bevacizumab+chemotherapy versus chemotherapy alone in elderly patients with untreated metastatic colorectal cancer: A randomized phase II trial—PRODIGE 20 study results. Ann Oncol. 2018; 29: 133-8.
10. Cassidy J, Saltz LB, Giantonio BJ, Kabbinavar FF, Hurwitz HI, Rohr UP. Effect of bevacizumab in older patients with metastatic colorectal cancer: Pooled analysis of four randomized studies. J Cancer Res Clin Oncol. 2010; 136: 737-43.
11. Tuca A, Gallego R, Ghanem I, Gil-Raga M, Feliu J. Chemotherapy and targeted agents in the treatment of elderly patients with metastatic colorectal cancer. J Clin Med. 2020; 9: 4015.
12. Muss HB, Berry DA, Cirrincione C, Budman DR, Henderson IC, Citron ML, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. J Clin Oncol. 2007; 25: 3699-704.
13. Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med. 2001; 345: 1091-7.
14. Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyrhasrdt JA, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA. 2017; 317: 2392-401.
15. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol. 2014; 32: 2240-7.

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# Sonar Mining of Deeply Located Foreign Bodies in the Musculoskeletal System

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## ABSTRACT

**Introduction:** Foreign body (FB) injuries constitute an important part of admission to emergency and orthopedic clinics in daily practice. The localization and removal of FBs can be difficult. Ultrasound (USG) plays an important role in the localization of FBs. In this study, we aimed to present the results of patients who underwent US-guided FB extraction.

**Methods:** Fifty-seven patients who were admitted to the emergency service and orthopedic outpatient clinic due to FB trauma to soft tissue were retrospectively evaluated. USG-guided removal was performed under local anesthesia. The number, size, shape, structure, distance to the skin, and integrity of the FB were determined using USG guidance. Patient satisfaction was evaluated with Roles-Maudsley score.

**Results:** The mean duration of surgery was 7 min (range; 5 to 20 minutes), and the mean incision size was 11 mm (range; 5 to 25 mm). Forty-seven of the patients underwent an outpatient procedure and were discharged on the same day. No postoperative complications were observed. Fifty one of 57 (89.5%) were very satisfied with the surgery.

**Conclusion:** Consequently, USG-guided FB extraction is a safe, fast, and comfortable option for the patient and the physician. Orthopedic physicians should receive USG training starting from their assistantship, and its use in daily practice should be increased.

**Keywords:** Ultrasound, soft tissue, foreign body

## Introduction

Foreign body (FB) injuries constitute an important part of admission to emergency and orthopedic clinics in daily practice. While most of them are superficial and palpable, some are located deeply. FB that penetrates the soft tissue in the musculoskeletal system may remain asymptomatic for a long time, as well as cause different symptoms and complications. Pain, abscess formation, tendon irritation, neurovascular damage, inflammatory reaction, and necrotizing fasciitis are some of the symptoms (1-4).

Radiographs can be useful for localization and are often used as part of initial evaluation. Radiopaque objects such as metals, shrapnel, and glass fragments can be seen on plain radiographs; radiolucent objects such as wood, splinters, and plastics may not be visible (5). The localization and removal of deeply located and radiolucent FBs that cannot be palpated can be difficult. Ultrasound (USG) plays an important role in the localization of these FB (6).

Although superficial, palpable FBs can be easily removed under emergency and outpatient clinic conditions, deep penetrating and non-palpable FBs may need to be extracted under operating room conditions (7).

Fluoroscopy is also frequently used for the localization and removal of radiopaque objects. The patient and surgical team may be exposed to radiation (8). The aim of this study was to present the results of patients who underwent USG-guided FB removal.

## Methods

Sixty-one consecutive patients (34 men, 27 women) who were admitted to the emergency service or orthopedic outpatient clinic due to FB trauma to soft tissue were evaluated. Four patients were lost during follow-up. In 53 of the 57 remaining patients, the reason for admission was persistent pain, whereas in three patients, it was the feeling of discomfort caused by the presence of FB. In one patient, FB was removed for forensic reasons. Before the intervention, 44 patients had X-ray imaging. However, X-ray imaging was not available for 13 patients. Among those with X-ray imaging, three underwent computed tomographies (CT) as supplementary imaging, while one patient without X-ray imaging underwent magnetic resonance imaging (MRI).

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Diagnostic USG was performed by the radiologist in all patients, and USG-guided surgery was recommended for patients with confirmed FB presence. The number, size, shape, structure, distance to the skin, and integrity of the FB were determined with USG-guidance (Table 1).

FB that could not be palpated at a depth of at least 10 mm, localized in the lower or upper extremities were included in the study. Objects that are superficial (10 mm > depth) and/or felt by palpation excluded from the study.

The surgery was performed under sterile conditions in emergency or outpatient intervention rooms using local anesthesia in 45 patients who could tolerate it. For 12 patients who either did not want or could not tolerate local anesthesia, the procedure was conducted in the operating room. Among these patients, sedation was administered to seven, spinal anesthesia to three, and general anesthesia to two. Post-operative control X-rays were taken for patients who underwent surgery due to radiopaque FB; however, no examination was requested for those with radiolucent FB. After the intervention, patients were monitored until wound healing and suturing was performed. Satisfaction assessment was conducted using the Roles-Maudsley questionnaire during the second month of follow-up (Table 2) (9).

First of all, the localization of the FB was visualized by USG. The surgical area was sterilely prepped with a povidone iodine solution. The USG probe was covered with a sterile sheath. Local anesthesia was applied at the site of FB. Then, the guide needle tip was sent to the FB using USG guidance (Figure 1). Without removing the guide needle, a minimal incision was made at the needle insertion point into the skin. Blunt dissection was observed along the needle trace, and the FB was reached. The FB is held along its long axis with the help of a clamp or grasper and then removed. Fluoroscopy was not used in any of the cases (Figure 2, 3).

High-resolution USG was performed by a radiologist with an experience of more than 10 years in USG and two orthopedic surgeons with an experience of 3 years (M.A.Ç., B.K.). The study was conducted using a GE Logiq P5 USG machine.

This study was approved by the İstanbul Medipol University Ethical Committee approval number: 190, date: 18.02.2021). All patients provided written informed consent.

### Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 29.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics, including means, minimums, and maximums, were examined to gain insights into the central tendency and variability of the variables under investigation.

## Results

The mean age of the patients was 22 (range; 2 to 62). Twenty-seven of the patients were women, and 30 were men. The mean time between the penetration of the FB and surgical intervention was 74 days (range; 1 day to 2 years). Thirteen patients developed abscesses around the FB. The area where the FB penetrated was the foot in 26 patients, hand in 19, knee in four, cruris in three, elbow in two, forearm in one, hip in one, and thigh in one (Table 1).

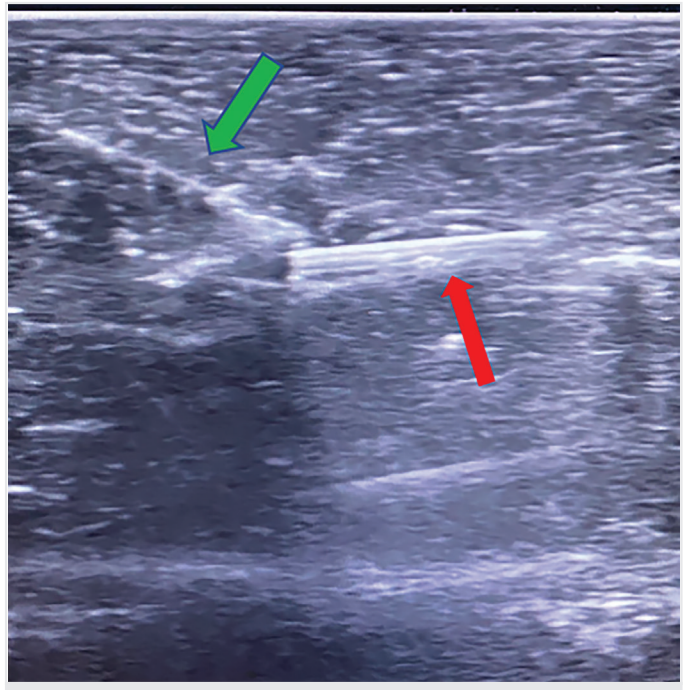

**Figure 1.** Foreign body (needle) indicated by a red arrow. Guide needle shown with green arrow

**Table 1. Characteristics of the foreign bodies according to localizations**

| Localization | n (%) | Width (mm) | Length (mm) | Depth (mm) | Time (min) | Incision (mm) |
|---|---|---|---|---|---|---|
| Foot | 26 (45.6) | 2.7 (0.8-15) | 16.5 (3-27) | 17.3 (10-35) | 7.5 (5-20) | 11 (6-25) |
| Hand | 19 (33.3) | 1.8 (0.7-3) | 10 (2-40) | 11.8 (10-15) | 6.7 (5-15) | 8.4 (6-10) |
| Knee | 4 (7) | 1.4 (0.7-3) | 18.2 (3-25) | 23.7 (15-30) | 9.5 (5-15) | 16.2 (5-25) |
| Cruris | 3 (5.2) | 1.3 (1-2) | 16 (3-40) | 33 (30-40) | 7 (5-10) | 13 (8-20) |
| Elbow | 2 (3.5) | 0.9 (0.8-1) | 14 (10-18) | 25 (20-30) | 8 (5-11) | 14 (8-20) |
| Forearm | 1 (1.8) | 2 | 6 | 30 | 5 | 8 |
| Hip | 1 (1.8) | 1 | 12 | 7 | 11 | 20 |
| Thigh | 1 (1.8) | 5 | 11 | 40 | 15 | 25 |
| Total | 57 (100) | 2.2 | 13.9 | 18 | 7.5 | 11.1 |

n: Number, mm: Milimeter, min: Minute(s)

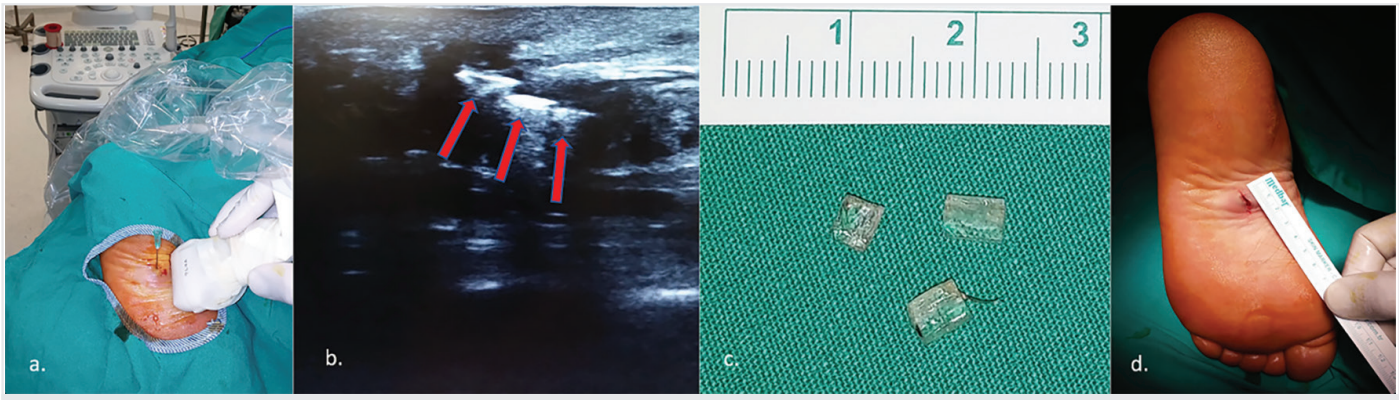


**Figure 2.** Ultrasound-assisted foreign body (glass pieces) removal from the left foot plantar area. (a, b) Localization of glass pieces under USG guidance (red arrows show the glass pieces), (c) Removed glass pieces, (d) 15 mm skin incision. (Written informed consent is taken from the patient)

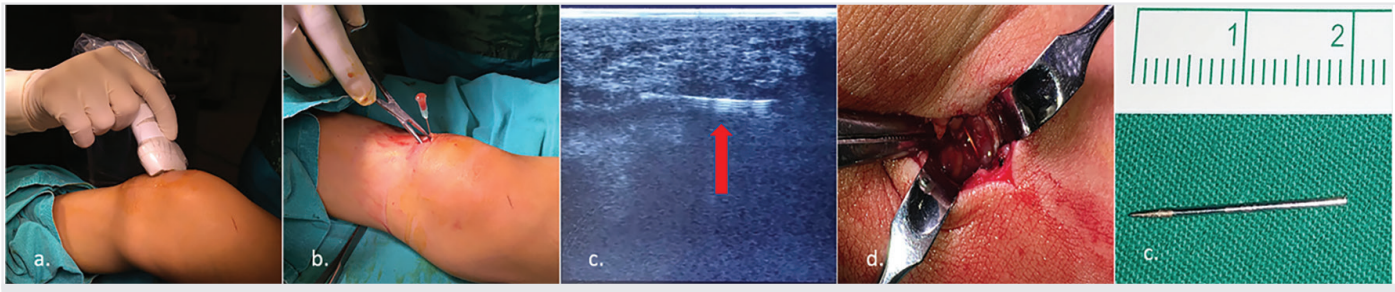


**Figure 3.** Ultrasound-assisted foreign body (needle) removal from the anterior part of the knee, (a, b) Localization of needle under USG guidance, (c) Red arrow show the needle, (d) Approximately 13 mm skin incision, (e) Removed needle. (Written informed consent is taken from the patient)

**Table 2. Roles-Maudsley score**

| | Point | Interpretation |
|---|---|---|
| Excellent | 1 | No pain, full activity |
| Good | 2 | Occasional discomfort, full activity |
| Fair | 3 | Some discomfort after prolonged activity |
| Poor | 4 | Pain-limiting activity |

Three glass pieces were extracted from the foot of one patient (Figure 2). They were considered a single piece because of their close localization to each other. All FB were successfully removed. Local anesthesia was preferred mainly for the patients. Local anesthesia was applied to 45 patients, sedation to seven, spinal anesthesia to three, and general anesthesia to two patients.

The average depth of FB was 18 mm (range; 10 to 40 mm), and the average size was 2x14 mm (range; 2x2 mm to 15x25 mm). While 38 of the FB were metallic (sewing needle, bullet core, iron burr), 11 were wood (piece of wood, thorn, toothpick) and 8 of them were glass.

The mean duration of surgery was 7 minutes (range; 5 to 20 minutes), and the mean incision size was 11 mm (range; 5 to 25 mm). Forty-seven of the patients underwent an outpatient procedure and were discharged on the same day. Nine patients were discharged after hospitalization for one night and one patient for two nights. For patients with abscess, postoperative antibiotherapy was initiated. No postoperative complications were observed in any patient during follow-up period. At second month follow up, 51 patients (89.5%) were very satisfied (excellent) with the surgery, and six (11.5%) patients were satisfied (good).

## Discussion

Clinical examination may be insufficient for localization and removal of some FBs. Additional attempts may be required to locate and remove deeply located FBs with granulation tissue surrounding them. Under USG, 57 non-palpable FBs were removed from the patients.

On one hand, some FBs penetrating the body may not show any symptoms; on the other hand, some may present with symptoms such as pain, tingling, hematoma, abscess formation, numbness, and loss of motor function due to nerve compression and anxiety (2,7). Although the main complaint of the patients in our study was pain, three patients requested extraction because they wanted to get rid of the feeling of a FB in the body, although there were no clinical symptoms.

Plain radiography is the preferred imaging modality for patients with FB penetration. Although plain radiographs are sufficient to show the presence of most FB, advanced imaging methods are needed to determine the presence and localization of materials such as plastics and wood that are not radiopaque. CT and MRI can also be used for diagnosis. Because they are expensive test methods, they are not the first choice and are not indicated for every FB (10). For example, most metallic objects are contraindicated for MRI (6). USG is an inexpensive imaging method with high sensitivity and specificity. Sonography has a reported sensitivity of 95% for detecting FB. In addition, it provides real-time intervention (11). In our series, 45 patients had previously

undergone imaging. For the two cases in which glass was penetrated, CT was requested, and in one case, MRI was used for detecting FB.

Hyperechoic appearance and shadowing are US findings that suggest a FB. This tool can be used for preoperative FB localization and as a guide for real-time intervention. Different methods for removal of FB are defined before (12-14). In daily practice, the removal of deeply located radiopaque materials is often performed under fluoroscopy in operating rooms. Although the extraction of some objects can be done easily with fewer fluoroscopic imaging procedures, a long operation time, excessive labor, and exposure to high radiation volumes (fluoroscopy) may be required to remove some FBs (8). This may lead to increased incision size and further soft tissue damage. During the extraction of FB located close to the vessels and nerves, these structures may also be damaged. The use of USG has previously been described in the literature (15-17). Our technique can also be considered a modified version of these previously described methods. In this technique, the localization of the FB is first determined by USG. Then, the FB is reached with a relatively small incision with a guide needle tip, and the FB is removed. Thus, the surrounding tissues are minimally damaged. Thus, it is possible to remove objects in the neighboring areas of the vascular nerve without damaging these structures. No major vascular or neurological complications occurred in our series. Only one patient experienced numbness around the incision side in the second week. On the second month, he stated his complications were completely recovered. Two months after surgery, all patients had satisfactory outcomes.

One of the difficulties of this method is that performing USG requires experience (18). In our study, the measurements were conducted by an experienced radiologist, and interventions were performed by two orthopedic surgeons with three years of experience using USG.

Complications such as tendon irritation, neuroma, and neuropathy due to FB remaining in the body for a long time have been reported in the literature. In addition, objects that can move like a needle tip may migrate to surrounding tissues and cause tissue irritation (19). In our study, we observed that a broken sewing needle penetrating the sole of the foot migrated between the metatarsals within two weeks. After localization with USG, the needle tip was extracted through an incision without damaging the tendon and vascular nerve package. Neurovascular deficit was not observed in the patient's follow-up period.

The monthly radiation exposure of an orthopedic resident doctor in trauma rotation was 79 mrem/month, and an orthopedic surgeon dealing with trauma and deformity was reported to be exposed to radiation of 53 mrem/month (20). One of the most important advantages of USG-guided procedures is that no need for fluoroscopy. During the procedure, the patient is exposed to radiation only during the first presentation and postoperative control radiographs. Thus, the amount of radiation to which both the patient and performer are exposed/to be exposed is reduced.

Another advantage of USG-guided FB removal is that it shortens the operation time and reduces the use of the operating room, thus reducing the cost. The average operating room usage fees in the United States are 35-36 dollars according to 2018 data (21). In our study, although the mean intervention duration was 7 min, only 12 of the 57 patients underwent the intervention under operating room conditions. The reasons for this are that patients do not want isolated local anesthesia, prefer a different anesthesia method, or are too young to tolerate local anesthesia.

### Study Limitation

Our study also has some limitations. This was a retrospective study with a small sample size. Another significant limitation was the incomplete X-ray imaging of the 13 patients. This circumstance may have led to the oversight of the accompanying pathologies. Additionally, we did not have a control group with the same/similar traumas, which limits us from comparing our results with those of other treatment methods.

## Conclusion

USG-guided FB extraction is a safe, fast, and comfortable option for patients and physicians. It should be preferred more in orthopedic practice. For this orthopedic physicians should receive USG training starting from their assistantship, and its use in daily practice should be increased. New multicenter studies involving larger sample sizes should be conducted to better demonstrate the effectiveness of this approach.

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**Ethics Committee Approval:** This study was approved by the İstanbul Medipol University Ethical Committee approval number: 190, date: 18.02.2021).

**Informed Consent:** All patients provided written informed consent.

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

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## References

1. Levine MR, Gorman SM, Young CF, Courtney DM. Clinical characteristics and management of wound foreign bodies in the ED. Am J Emerg Med. 2008; 26: 918-22.
2. Yanay O, Vaughan DJ, Diab M, Brownstein D, Brogan TV. Retained wooden foreign body in a child's thigh complicated by severe necrotizing fasciitis: a case report and discussion of imaging modalities for early diagnosis. Pediatr Emerg Care. 2001; 17: 354-5.
3. Choudhari KA, Muthu T, Tan MH. Progressive ulnar neuropathy caused by delayed migration of a foreign body. Br J Neurosurg. 2001; 15: 263-5.
4. Turker M, Basbug V, Kesik K, Turkmen F, Kacira BK, Korucu IH, et al. Evaluation of deep-seated soft tissue foreign bodies according to gender and age groups. Selcuk Med J. 2019; 1: 24-30.

5. Hunter TB, Taljanovic MS. Foreign bodies. Radiographics. 2003; 23: 731-57.

6. Mohammadi A, Ghasemi-Rad M, Khodabakhsh M. Non-opaque soft tissue foreign body: sonographic findings. BMC Med Imaging. 2011; 11: 9.

7. Zhu Q, Chen Y, Zeng Q, Zhao J, Yu X, Zhou C, et al. Percutaneous extraction of deeply-embedded radiopaque foreign bodies using a less-invasive technique under image guidance. J Trauma Acute Care Surg. 2012; 72: 302-5.

8. Müller LP, Suffner J, Wenda K, Mohr W, Rommens PM. Radiation exposure to the hands and the thyroid of the surgeon during intramedullary nailing. Injury. 1998; 29: 461-8.

9. Roles NC, Maudsley RH. Radial tunnel syndrome: resistant tennis elbow as a nerve entrapment. J Bone Joint Surg Br. 1972; 54: 499-508.

10. Flom LL, Ellis GL. Radiologic evaluation of foreign bodies. Emerg Med Clin North Am. 1992; 10: 163-77.

11. Ober CP, Jones JC, Larson MM, Lanz OI, Werre SR. Comparison of ultrasound, computed tomography, and magnetic resonance imaging in detection of acute wooden foreign bodies in the canine manus. Vet Radiol Ultrasound. 2008; 49: 411-8.

12. Uludağ A, Tosun HB, Çiçek N, Şirik M, Uludağ Ö, Atiç R. Surgical approach to foreing bodies observed in the soft tissue of extremities after injury. Dicle Med J. 2019; 46: 215-23 (Turkish).

13. Dülgeroğlu TC, MetiNeren H, Aydin E, Dülgeroğlu A. A conscious patient: taking a foreign object out with the help of a magnet: case report. Turkiye Klinikleri J Case Rep. 2016; 24: 344-7.

14. Bilgin Y, Birisik F. Retrospective analysis of puncture wounds with retained foreign bodies in the extremities requiring surgical intervention. Med-Science. 2021; 10: 416.

15. Tantray MD, Rather A, Manaan Q, Andleeb I, Mohammad M, Gull Y. Role of ultrasound in detection of radiolucent foreign bodies in extremities. Strategies Trauma Limb Reconstr. 2018; 13: 81-5.

16. Rooks VJ, Shiels WE 3rd, Murakami JW. Soft tissue foreign bodies: a training manual for sonographic diagnosis and guided removal. J Clin Ultrasound. 2020; 48: 330-6.

17. Hiremath R, Reddy H, Ibrahim J, Haritha CH, Shah RS. Soft tissue foreign body: utility of high-resolution ultrasonography. J Clin Diagn Res. 2017; 11: TC14-6.

18. Orlinsky M, Knittel P, Feit T, Chan L, Mandavia D. The comparative accuracy of radiolucent foreign body detection using ultrasonography. Am J Emerg Med. 2000; 18: 401-3.

19. Devgan A, Mudgal KC. An unusual case of foreign body knee that spontaneously migrated inside and out of the joint: arthroscopic removal. Knee Surg Sports Traumatol Arthrosc. 2007; 15: 758-60.

20. Gausden EB, Christ AB, Zeldin R, Lane JM, McCarthy MM. Tracking cumulative radiation exposure in orthopaedic surgeons and residents: what dose are we getting? J Bone Joint Surg Am. 2017; 99: 1324-9.

21. Childers CP, Maggard-Gibbons M. Understanding costs of care in the operating room. JAMA Surg. 2018; 153: e176233.

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# Night-Eating Syndrome, Sleep Quality, and Eating Mindfulness in Psychiatric Outpatients

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## ABSTRACT

**Introduction:** This study aimed to determine eating mindfulness (EM), night eating syndrome (NES), and sleep quality in adult subjects presenting to a psychiatric outpatient clinic and to evaluate possible differences according to diagnoses and clinical variables.

**Methods:** This study included 381 outpatients. Sociodemographic data were collected, the Night Eating Questionnaire (NEQ), Pittsburgh Sleep Quality Index (PSQI), and the Mindful Eating Questionnaire (MEQ) were completed, and body mass index was measured.

**Results:** The median PSQI score was 3.0 (0.0-7.0), the median NEQ total score was 4.0 (0.0-14.0), and the median MEQ total score was 76.0 (59.0-95.0). Sixteen percent of the participants met the NES criteria. The patient group with the poorest sleep quality was the group with alcohol/substance use disorder and atypical psychosis. The patient groups with the lowest EM were those with schizophrenia, impulse control disorder, attention deficit disorder, and hyperactivity disorder. The highest NEQ score was found in individuals diagnosed with alcohol/substance use disorder. As the NEQ scores increased, so did the PSQI. A significant negative correlation was found between NEQ and MEQ total, disinhibition, emotional eating, eating control, and focus. The PSQI ($\beta$=1.169, $p<0.001$) and the eating control subdimension ($\beta$=-0.425, $p=0.003$) predicted the NEQ scale.

**Conclusion:** NES should not be underestimated in psychiatric outpatient clinics. EM, NES, and sleep quality are closely related. Regarding patients' eating attitudes, sleep problems in psychiatric disorders should also be considered. The eating habits and attitudes of these patients must be carefully examined, and appropriate individuals must be targeted for mindfulness training.

**Keywords:** Eating behavior, mental disorders, mindful eating, night eating syndrome, sleep quality

## Introduction

Night eating syndrome (NES), which is characterized by morning anorexia, evening hyperphagia, and insomnia, is more common than expected in patients presenting to a psychiatric outpatient clinic. Although NES was first described in patients with treatment-resistant obesity, it is also common in non-obese individuals (1). The prevalence of NES is estimated at 1.5% in the general population (2). NES is associated with stress, neuroticism, depression, and anxiety disorders (3-5). The serotonergic system and circadian rhythm disturbances are thought to be responsible for its development (6). Normally, the circadian rhythms of eating and sleep are synchronized. However, in individuals with NES, a phase delay of approximately 2 to 6 hours between eating and sleep rhythms. Food eaten at night disrupts sleep rhythms and can lead to insomnia (difficulty falling asleep and maintaining sleep). This leads to negative mental effects (especially mood and anxiety disorders) and negative metabolic effects. The imbalance between ghrelin and leptin that occurs in these individuals can lead to overeating behaviors (7). Similarly, sleep disorders may affect eating behavior and diet composition, leading to high caloric intake. Eating mindfulness (EM) may be an important factor in the relationship between night eating and sleep.

EM is food-oriented eating by individuals who are aware of their eating habits, mental thoughts, and hunger and satiety signals during eating without being affected by environmental factors. In EM, the person stops the action as soon as they sense a feeling of fullness by noticing internal bodily signals, thus preventing them from eating in situations that encourage them to eat (8). Developing this ability helps people to control their weight and deal with sudden food cravings. It also appears to be effective, especially in improving disordered eating behaviors, such as NES, weight control, and mental health (9).

There is research showing that NES is related to sleep and stress and can affect sleep quality and eating awareness (10). Night eating negatively affects sleep, weight, and metabolism and can cause chronic medical problems, as do inactivity and side effects of psychotropic drugs (6). We

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believe that NES, an eating disorder, and EM are important in psychiatric patients who are vulnerable to the metabolic side effects of psychotropic drugs. NES itself and low EM may result in overweight or obesity and may interfere with psychiatric treatment. A person's sleep quality and NES can be affected by EM. It has been reported that the prevalence of NES among individuals with psychiatric disorders is higher than expected (11). A previous study investigating the prevalence of NES in patients diagnosed with major depressive disorder highlighted the prevalence of this syndrome in relation to psychiatric disorders (12). Recognizing NES and sleep disorders accompanying psychiatric disorders and identifying inappropriate eating habits allows the treatment team to modify their approaches to improve patient adherence to treatment and reduce future complications. The aim of this study was to determine EM, NES, and sleep quality in adult patients presenting to psychiatric outpatient clinics and to evaluate potential differences in these variables according to various psychiatric diagnoses and clinical features. This study was designed to understand how participants differ in terms of psychiatric diagnoses, symptoms, medication use, and other clinical variables. Additionally, this study aimed to comprehend the relationships between EM, NES, and sleep quality and how these variables mutually influence each other. This comprehensive study will be an important step towards a deeper understanding of the effects of psychiatric disorders and sleep problems on eating behaviors.

## Methods

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 56, date: 11.02.2022). The study was conducted between March 2022 and June 2022 at the psychiatric outpatient clinic of University of Health Sciences Turkey, İstanbul Training and Research Hospital after ethical approval was granted.

All subjects who presented to the psychiatric outpatient clinic and met the inclusion criteria were included in the study. The presence of psychiatric disorders was determined by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Written informed consent was obtained from all participants, and the sociodemographic data forms, the Night Eating Questionnaire (NEQ), the Pittsburgh Sleep Quality Index (PSQI), and the Mindful Eating Questionnaire (MEQ) were completed for all. After completing the scales, the weight of all participants was measured using a Medisana brand digital scale, height was measured using a tape measure without shoes, and body mass index (BMI) was calculated.

### Sample

This study involved 381 outpatients who met the study criteria and presented to the Outpatient Clinic of Psychiatry, University of Health Sciences Turkey, İstanbul Training and Research Hospital. Throughout the study process, 453 individuals were identified; however, those who did not complete the scales were excluded from the study. The inclusion criteria for the participants were as follows: age between 18 and 65 years, no significant physical or neurological pathology preventing completion of the scales, no dementia/cognitive dysfunction, no mental retardation, no known sleep disorders such as narcolepsy, hypersomnia, sleep terrors, and none of the diagnoses eating disorders, and signing of informed consent. There was no control group in the study.

### Measures

**Sociodemographic Data Form:** This semi-structured scale was created by the researchers and asked all participants about age, gender, education status, working status, cigarette, alcohol, and drug use, known chronic diseases, medications taken continuously, diet and exercise, BMI, and known psychiatric treatments.

**Night Eating Questionnaire:** This questionnaire was developed by Allison et al. (13) and was adapted into Turkish by Atasoy et al. (14). The total score ranged from 0 to 52, and those who scored 30 or more points on the scale were considered at risk. In the validity and reliability study of the Turkish version, the cutoff value was assumed to be 18 points.

**Mindful Eating Questionnaire:** This questionnaire was developed by Framson et al. (15), and its Turkish validity and reliability were studied by Köse et al. (16). The scale includes seven subdimensions: disinhibition, emotional eating, eating control, focus, eating discipline, mindfulness, and interference. A high value for each subdimension of the scale indicates that the trait associated with that subdimension is high. The lowest score was 30 and the highest score was 150. The higher the score on the scale, the higher the level of EM.

**Pittsburgh Sleep Quality Index:** The Turkish validity and reliability of the 19-item scale were examined. The total score ranged from 0 to 21, and a score of more than 5 points on the scale indicates poor sleep quality (17).

### Statistical Analysis

Analyses were performed using 22 package programs from SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). Descriptive data were reported in the study as n and percentage values for categorical data and as mean ± standard deviation and median interquartile range (25-75 percentile values) for continuous data. Chi-square analysis (Pearson's chi-square) was used to compare categorical variables between groups. The conformity of constant variables to the normal distribution was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare paired groups, and the Kruskal-Wallis test was used to compare more than two variables. The Spearman's correlation test was used to examine the relationship between continuous variables. Linear regression analysis was performed to identify the predictors of the NEQ scale scores. The enter method was used to construct the model. The statistical significance level in the analyses was taken as $p<0.05$.

## Results

A total of 381 participants with a mean age of 39.3±14.1 (minimum: 18-maximum: 65) years were included in the study. A total of 65.4% of participants were female and 34.6% were male. A total of 43.6% of participants were single, 56.4% were married, 27.3% had an elementary school degree, 27% had a secondary school degree, and 45.7% had a high school degree. A total of 92.9% of participants had an active psychiatric

disorder and 69.6% were receiving active psychiatric treatment. Thirty-two percent of participants had a family history of psychiatric disorder, 9.2% had a history of self-injurious behavior, 15% had a history of suicide attempts, and 34.1% had a history of additional organic disease.

Forty-two percent of participants reported skipping at least one meal per day (44.4% of the 160 individuals in the morning, 43.8% in the afternoon, and 11.9% in the evening), 35.7% reported consuming junk food between meals, and 52.5% reported engaging in physical activity (with frequencies ranging from daily to three or four times per month). 40.7% of participants had dieted at some point in their lives, and 23.1% of participants had a family member with obesity in their family history. 5.8% of participants reported that they were planning bariatric surgery for themselves (Table 1).

When all participants were examined, the median PSQI score was 3.0 (0.0-7.0), the median NES score was 4.0 (0.0-14.0), and the median MEQ total score was 76.0 (59.0-95.0).

The scale scores by sociodemographic and clinical characteristics are compared in Table 2. To mention only some of them: PSQI ($p<0.001$) and NEQ ($p<0.001$) scores of individuals with active psychiatric disorder were significantly higher than those of individuals without psychiatric disorder, and the MEQ scores ($p=0.015$) were significantly lower. The PSQI ($p<0.001$) and NEQ ($p=0.001$) scores of those who received psychiatric treatment were significantly higher than those of those who did not, and the MEQ scores ($p=0.023$) were significantly lower. The PSQI ($p<0.001$) and NEQ ($p=0.001$) scores of those who skipped meals were significantly higher than those who did not. The PSQI ($p<0.001$) and NEQ ($p<0.001$) scores of those who consumed junk food between meals were significantly higher than those who did not, and the MEQ score ($p=0.04$) was significantly lower. The PSQI score ($p=0.025$) of those who engaged in regular physical activity was significantly lower than that of those who did not, and the MEQ score ($p=0.001$) was significantly higher. The MEQ score of those who had a family member with obesity in their family history was significantly lower than that of those who did not have a family member ($p=0.025$) (Table 2).

The highest PSQI scores were found in those diagnosed with alcohol and drug use disorders and those diagnosed with atypical psychosis. Subjects diagnosed with alcohol and substance use disorder had the highest NEQ score. The lowest MEQ score was observed in individuals diagnosed with schizophrenia, impulse control disorder, and attention deficit and hyperactivity disorder (ADHD) (Table 3).

The results of the correlation analysis are presented in Table 4. Accordingly, there was a positive correlation between BMI and PSQI and NEQ and a negative correlation between BMI and MEQ total, disinhibition, emotional eating, eating control, and focus. A positive correlation was found between PSQI and MEQ and a negative correlation was found between PSQI and MEQ total, disinhibition, emotional eating, eating control, focus, and interference. A significant negative correlation was found between NEQ and MEQ total, disinhibition, emotional eating, eating control, and focus (Table 4).

After multiple linear regression analysis, the PSQI ($\beta=1.169$, $p<0.001$) and the eating control subdimension ($\beta=-0.425$, $p=0.003$) predicted the NEQ scale (Table 5).

## Discussion

According to our study results, 34.9% of participants had poor sleep quality when the PSQI cutoff score was 5. It should be noted that 92.9% of the participants had an active psychiatric disorder, and 69.6% were receiving active psychotropic medications, including hypnotic and sedative drugs. The sleep quality of individuals with a psychiatric diagnosis was significantly poorer than that of individuals without such a diagnosis. In addition, those with any diagnosis had lower EM scores and higher NEQ scores. The sleep quality of patients with alcohol and drug use disorders and atypical psychosis was poorer than that of other psychiatric diagnoses. Insomnia is associated with high comorbidity, particularly depression, anxiety disorders, schizophrenia, and alcohol and drug use disorders. NES is often associated with psychiatric comorbidities. Psychiatric disorders trigger the occurrence of NES (1). In a study that included psychotic disorders, 16.5% of patients were diagnosed with NES according to the NEQ (the cut-off point was assumed to be 25) (18). In a study of 175 patients with schizophrenia, NES was found to be 8% associated with poor sleep quality according to the PSQI (19).

In addition to the metabolic side effects of psychotropic drugs, high BMI is an expected outcome in psychiatric patients because it is also associated with EM. The participants were overweight with a mean BMI of 25.6. On the other hand, the EM and sleep quality were lower in those who received psychotropic drugs than in those who did not. We hypothesized that the low EM of drug users may be due to their psychiatric disorders. This is because a psychiatric diagnosis may have a negative impact on eating behavior. There is very little research on this topic. Regardless of psychiatric disorders, treatment with psychotropic drugs can affect sleep-wake cycles. Psychotropic drugs can improve sleep by increasing the activity of systems that provide sleep or improve wakefulness by using vice versa mechanisms. We do not know whether this finding is due to the use of psychotropic drugs, including the use of multiple drugs, or the disease itself.

In our study group, 16% of participants (at 18 cut-off points) met the NES criteria. This rate is consistent with the data reported in the literature. NES occurs in approximately 12.3% of psychiatric patients (20). The NEQ score was highest among patients diagnosed with substance and alcohol use disorders, with a median score of 11 points. It has been noted that people with alcohol/substance use disorders have high rates of eating disorder behaviors due to shared biological and psychological risk factors (21). Both have common denominators, such as impulsivity, compulsive behavior, the tendency to eat to cope with negative emotions, and the tendency to avoid emotions.

The patient groups with the lowest EM were those diagnosed with schizophrenia, impulse control disorders, and ADHD in the present study. EM has been studied primarily in the general population and in individuals with obesity rather than those with eating disorders. Therefore, very few data are available to make a comparison. The risk of developing an eating disorder is almost three times higher in individuals with ADHD than in the general population (22). Mindful eating indicates that the individual chooses and is aware of the appropriate foods and is related to self-efficacy in eating. The ability to be mindful is associated

**Table 1. Sociodemographic and clinical characteristics of the participants**

| | | Number | % |
|---|---|---|---|
| Age (years), mean ± SD | | 39.3±14.1 | |
| BMI, mean ± SD | | 25.6±4.6 | |
| Gender | Female | 249 | 65.4 |
| | Male | 132 | 34.6 |
| Marital status | Single | 166 | 43.6 |
| | Married | 215 | 56.4 |
| Education status | Elementary school degree | 104 | 27.3 |
| | Secondary school degree | 103 | 27.0 |
| | High school degree | 174 | 45.7 |
| Place of residence | Village-town | 65 | 17.1 |
| | City | 316 | 82.9 |
| Economical status | Below the hunger line | 12 | 3.1 |
| | Below the poverty line | 190 | 49.9 |
| | Above the poverty line | 179 | 47.0 |
| Working status | Working | 160 | 42.0 |
| | Not working | 221 | 58.0 |
| Alcohol/substance use | Yes | 40 | 10.5 |
| | No | 341 | 89.5 |
| Cigarette use | Yes | 118 | 31.0 |
| | No | 263 | 69.0 |
| Active psychiatric disorder | Yes | 354 | 92.9 |
| | No | 27 | 7.1 |
| Status of receiving psychiatric treatment | Yes | 265 | 69.6 |
| | No | 116 | 30.4 |
| A family history of psychiatric disorder | Yes | 123 | 32.3 |
| | No | 258 | 67.7 |
| A history of self-injurious | Yes | 35 | 9.2 |
| | No | 346 | 90.8 |
| A history of suicide attempts | Yes | 57 | 15.0 |
| | No | 324 | 85.0 |
| A history of additional organic disease | Yes | 130 | 34.1 |
| | No | 251 | 65.9 |
| Skipping at least one meal per day | Yes | 160 | 42.0 |
| | No | 221 | 58.0 |
| Consuming junk food between meals | Yes | 136 | 35.7 |
| | No | 245 | 64.3 |
| Engaging in physical activity | Yes | 200 | 52.5 |
| | No | 181 | 47.5 |
| Physical activity pattern | Daily | 36 | 18.0 |
| | 3-4 times per week | 38 | 19.0 |
| | 1-2 times per week | 57 | 28.5 |
| | 1-2 times per month | 69 | 34.5 |
| Dieting effort at some point in their lives | Yes | 155 | 40.7 |
| | No | 226 | 59.3 |
| Having a family member with obesity in their family history | Yes | 88 | 23.1 |
| | No | 293 | 76.9 |
| Planning bariatric surgery for themselves | Yes | 22 | 5.8 |
| | No | 359 | 94.2 |

BMI: Body mass index, SD: Standard deviation

**Table 2. Comparison of scale scores according to sociodemographic and clinical characteristics**

| | | PSQI | | NEQ | | MEQ | |
|---|---|---|---|---|---|---|---|
| | | Median (IQR) | p | Median (IQR) | p | Median (IQR) | p |
| Gender | Female | 3.0 (0.0-8.0) | **0.021** | 4.0 (0.0-14.0) | 0.344 | 77.0 (60.0-95.0) | 0.330 |
| | Male | 2.0 (0.0-6.0) | | 3.0 (0.0-11.0) | | 71.5 (57.0-95.0) | |
| Marital status | Single | 3.0 (0.0-7.0) | 0.375 | 4.0 (0.0-15.0) | 0.208 | 76.0 (57.0-95.0) | 0.813 |
| | Married | 2.0 (0.0-7.0) | | 3.0 (0.0-12.0) | | 76.0 (59.0-94.0) | |
| Education status | Elementary school degree | 3.0 (0.0-7.5) | 0.716 | 3.0 (0.0-12.5) | 0.496 | 80.0 (63.0-97.5) | 0.316 |
| | Secondary school degree | 3.0 (0.0-8.0) | | 4.0 (0.0-13.0) | | 72.0 (57.0-95.0) | |
| | High school degree | 3.0 (0.0-7.0) | | 4.0 (0.0-15.0) | | 74.0 (59.0-94.0) | |
| Place of residence | Village-town | 1.0 (0.0-6.0) | 0.052 | 1.0 (0.0-7.0) | **0.004** | 70.0 (55.0-93.0) | 0.065 |
| | City | 3.0 (0.0-8.0) | | 4.0 (0.0-14.0) | | 78.0 (60.0-95.0) | |
| Economical status | Below the hunger line | 2.0 (0.0-10.0) | 0.814 | 1.5 (0.0-20.5) | 0.834 | 72.5 (58.5-90.5)[a,b] | **0.037** |
| | Below the poverty line | 3.0 (0.0-7.0) | | 4.0 (0.0-14.0) | | 80.0 (64.0-98.0)[a] | |
| | Above the poverty line | 3.0 (0.0-7.0) | | 3.0 (0.0-12.0) | | 71.0 (57.0-90.0)[b] | |
| Working status | Working | 2.0 (0.0-6.0) | **0.008** | 3.0 (0.0-11.0) | **0.033** | 78.0 (63.5-95.5) | 0.157 |
| | Not working | 3.0 (0.0-8.0) | | 4.0 (0.0-14.0) | | 74.0 (57.0-94.0) | |
| Alcohol/substance use | Yes | 1.0 (0.0-5.0) | 0.188 | 3.0 (0.0-14.0) | 0.908 | 67.0 (55.0-88.5) | 0.132 |
| | No | 3.0 (0.0-8.0) | | 4.0 (0.0-13.0) | | 77.0 (59.0-95.0) | |
| Cigarette use | Yes | 3.0 (0.0-8.0) | 0.078 | 5.0 (0.0-16.0) | **0.036** | 66.0 (52.0-91.0) | **0.011** |
| | No | 2.0 (0.0-7.0) | | 3.0 (0.0-12.0) | | 78.0 (64.0-96.0) | |
| Active psychiatric disorders | Yes | 3.0 (0.0-8.0) | **<0.001** | 4.0 (0.0-14.0) | **<0.001** | 74.0 (58.0-94.0) | **0.015** |
| | No | 0.0 (0.0-0.0) | | 0.0 (0.0-0.0) | | 84.0 (75.0-103.0) | |
| Status of psychiatric treatment | Yes | 3.0 (0.0-8.0) | **<0.001** | 5.0 (0.0-14.0) | **0.001** | 72.0 (57.0-94.0) | **0.023** |
| | No | 1.0 (0.0-6.0) | | 1.0 (0.0-10.5) | | 80.5 (65.0-97.0) | |
| Family history of psychiatric disorders | Yes | 4.0 (0.0-9.0) | **0.006** | 6.0 (1.0-17.0) | **<0.001** | 66.0 (52.0-85.0) | **<0.001** |
| | No | 2.0 (0.0-7.0) | | 2.0 (0.0-11.0) | | 80.0 (64.0-98.0) | |
| History of self-injurious | Yes | 6.0 (2.0-9.0) | **0.008** | 7.0 (0.0-17.0) | 0.071 | 69.0 (59.0-82.0) | 0.149 |
| | No | 2.5 (0.0-7.0) | | 3.0 (0.0-12.0) | | 77.0 (59.0-95.0) | |
| History of suicide attempts | Yes | 5.0 (2.0-12.0) | **0.001** | 5.0 (0.0-15.0) | 0.175 | 66.0 (52.0-86.0) | **0.005** |
| | No | 2.0 (0.0-7.0) | | 3.0 (0.0-13.0) | | 78.0 (60.0-96.0) | |
| History of organic disease | Yes | 2.0 (0.0-7.0) | 0.357 | 1.0 (0.0-11.0) | **0.036** | 77.0 (57.0-96.0) | 0.784 |
| | No | 3.0 (0.0-7.0) | | 4.0 (0.0-14.0) | | 75.0 (60.0-94.0) | |
| Skipping at least one meal per day | Yes | 4.5 (0.0-9.0) | **<0.001** | 6.0 (0.0-16.0) | **0.001** | 75.5 (59.0-95.0) | 0.627 |
| | No | 2.0 (0.0-6.0) | | 2.0 (0.0-11.0) | | 77.0 (58.0-95.0) | |
| Skipped meal | Morning | 4.0 (0.0-9.0) | 0.198 | 6.0 (0.0-14.0) | 0.419 | 74.0 (61.0-95.0) | 0.768 |
| | Afternoon | 6.0 (1.0-10.0) | | 9.5 (0.0-17.0) | | 76.0 (59.0-97.0) | |
| | Evening | 3.0 (0.0-5.0) | | 4.0 (1.0-7.0) | | 77.0 (57.0-91.0) | |
| Consuming junk food between meals | Yes | 6.0 (2.0-9.0) | **<0.001** | 10.5 (2.0-18.0) | **<0.001** | 70.0 (57.0-94.0) | **0.04** |
| | No | 1.0 (0.0-6.0) | | 1.0 (0.0-9.0) | | 78.0 (62.0-96.0) | |
| Engaging in physical activity | Yes | 2.5 (0.0-6.0) | **0.025** | 3.0 (0.0-13.0) | 0.314 | 80.0 (63.0-97.5) | **0.001** |
| | No | 3.0 (0.0-8.0) | | 4.0 (0.0-14.0) | | 71.0 (56.0-89.0) | |
| Dieting effort at some point in their lives | Yes | 3.0 (0.0-8.0) | 0.162 | 4.0 (0.0-16.0) | 0.084 | 71.0 (58.0-90.0) | 0.052 |
| | No | 3.0 (0.0-6.0) | | 3.0 (0.0-12.0) | | 78.5 (59.0-98.0) | |
| Having a family member with obesity in their family history | Yes | 3.0 (0.0-8.0) | 0.809 | 4.0 (0.0-14.5) | 0.905 | 68.0 (57.5-88.0) | **0.025** |
| | No | 3.0 (0.0-7.0) | | 3.0 (0.0-13.0) | | 78.0 (61.0-97.0) | |
| Planning for bariatric surgery | Yes | 6.0 (0.0-12.0) | 0.062 | 7.0 (1.0-25.0) | 0.064 | 59.5 (51.0-94.0) | 0.191 |
| | No | 3.0 (0.0-7.0) | | 4.0 (0.0-13.0) | | 76.0 (59.0-95.0) | |

The Mann-Whitney U test was performed in paired groups, and the Kruskal-Wallis test was performed in more than two groups. [a,b]The group from which the difference originates. NEQ: Night Eating Questionnaire, PSQI: Pittsburgh Sleep Quality Index, MEQ: Mindful Eating Questionnaire

**Table 3. Scale scores according to the participants' primary psychiatric diagnoses**

| | PSQI | NEQ | MEQ total | n |
|---|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) | |
| Generalized anxiety disorder | 5.0 (2.0-8.0) | 8.0 (1.0-16.0) | 77.0 (62.0-98.0) | 71 |
| Panic disorder | 5.0 (1.0-8.0) | 9.0 (0.0-24.0) | 70.0 (63.0-79.0) | 15 |
| NOS-psychosis | 7.5 (3.0-11.0) | 9.5 (4.0-17.5) | 57.0 (45.0-69.5) | 16 |
| Schizophrenia | 8.0 (2.5-8.5) | 3.5 (2.5-6.0) | 47.5 (38.5-53.5) | 12 |
| Obsessive compulsive disorder | 2.0 (0.0-7.0) | 1.0 (0.0-14.0) | 85.0 (65.0-98.0) | 15 |
| Conversion disorder | 0.0 (0.0-6.0) | 0.0 (0.0-13.0) | 61.0 (53.0-98.0) | 11 |
| Somatic symptom disorder | 1.0 (0.0-6.0) | 0.0 (0.0-6.0) | 85.0 (72.0-97.0) | 15 |
| Depressive disorder | 5.5 (3.0-11.0) | 7.5 (2.0-14.0) | 73.5 (64.0-94.0) | 50 |
| NOS-anxiety disorder | 2.0 (0.0-8.0) | 3.0 (0.0-14.0) | 86.0 (60.0-100.0) | 55 |
| Dysthymic disorder | 0.0 (0.0-9.0) | 0.0 (0.0-6.0) | 65.0 (57.0-94.0) | 11 |
| Bipolar disorder | 1.5 (0.0-5.5) | 4.0 (0.5-19.0) | 68.5 (59.5-87.5) | 12 |
| Alcohol and substance use disorders | 9.0 (9.0-9.0) | 11.0 (11.0-11.0) | 71.0 (71.0-71.0) | 1 |
| Impulse control disorders | 0.0 (0.0-1.0) | 0.0 (0.0-0.0) | 53.0 (46.0-66.0) | 5 |
| Social anxiety disorder | 0.0 (0.0-10.0) | 0.0 (0.0-14.0) | 93.0 (70.0-112.0) | 11 |
| Hypochondriasis | 1.0 (0.0-4.5) | 0.0 (0.0-9.0) | 92.0 (67.0-110.0) | 8 |
| NOS-mood disorder | 5.0 (2.0-8.0) | 11.5 (4.0-19.0) | 58.0 (53.0-61.0) | 10 |
| Attention-deficit/hyperactivity disorder | 0.0 (0.0-0.0) | 0.0 (0.0-26.0) | 55.0 (45.0-65.0) | 9 |
| Gender identity disorder | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 82.0 (82.0-82.0) | 1 |
| Adjustment disorder | 1.0 (0.0-2.0) | 1.0 (0.0-3.0) | 78.0 (68.0-82.0) | 11 |
| Posttraumatic stress disorder | 5.5 (4.0-10.0) | 10.5 (2.0-18.0) | 72.0 (37.0-80.0) | 6 |
| Agoraphobia | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 89.5 (81.0-97.0) | 4 |
| Acute stress disorder | 3.0 (3.0-4.0) | 8.0 (4.0-9.0) | 69.0 (66.0-84.0) | 5 |

NEQ: Night Eating Questionnaire, PSQI: Pittsburgh Sleep Quality Index, MEQ: Mindful Eating Questionnaire

with less impulsive eating, lower calorie consumption, and healthier food choices.

In addition to subgroups of diseases that were not separately examined in our study, ADHD patients might experience difficulties, particularly in the focus, eating control, and disinhibition subgroups of EM. Similarly, difficulties with disinhibition observed in schizophrenic patients might prevent them from being aware of the signals that initiate and terminate eating. Anhedonic states with disinhibition may reduce control over eating behavior and even lead individuals to choose palatable, high-carbohydrate foods. Although we are not certain, we believe that this finding is not solely due to the effects of psychotropic drugs on appetite and weight.

Those who skipped at least one meal per day and those who consumed junk food had poorer sleep quality and higher NES scores. In addition, those who consumed junk food had lower EM. Although studies have found low EM in individuals who skip meals (23), we did not find a significant association between these two factors. However, we found a significant difference between junk food consumption and EM. EM encompasses nutritious food choices, mindful awareness of the consequences of the foods consumed, and eating patterns that respond to hunger-satiety signals. Accordingly, the low EM observed in those who consumed extra junk food between meals was an expected outcome.

On the other hand, skipping breakfast in NES is expected. 18.6% of the participants skipping breakfast (42% skipped at least one meal). Sleep quality affects eating episodes. It was found that people with low sleep duration skipped breakfast more often than did normal people. It has been reported that people with low sleep duration skip meals, consume snacks in the form of junk food, and consume most of their food in the late evening or at night. The habit of eating junk food is associated with shorter sleep duration (24).

Individuals who reported engaging in regular physical activity had significantly better sleep quality and significantly higher EM than those who did not. Although participants' reports of physical activity ranged from "daily" to "1-2 times a month," physical activity level was not clearly measured in our study; however, it appears to influence both parameters. Physical activity regulates the stress response and helps control sleep quality and eating. It facilitates falling asleep and maintaining sleep, increases the depth of sleep, positively regulates the autonomic nervous system, and increases sleep quality through restful sleep (25). Physical activity has also been reported to influence eating behavior, eating timing, the amount of food consumed, and the selection of palatable and high-calorie foods, which is referred to as hedonic eating (26).

As the participants' BMI index increased, their sleep quality decreased, their night eating scores increased, and their EM decreased (they had less

disinhibition of eating, eating control, focus on eating, and emotional eating). This is, however, the result that we expected. A bidirectional interaction between weight gain and sleep. The timing and content of eating can influence our sleep duration and phases (27). Because the relationship between EM and BMI is well known, studies have also been conducted with EM training, and it was found that participants who received mindfulness training ate fewer calories and improved their control over their eating (28,29). Literature data consistent with our findings have shown us that there is a significant negative relationship between EM, its subdimension, and BMI (8,30). However, emotional eating is generally positively correlated with BMI, although it is usually not the only cause of being overweight. In the evaluation of the MEQ, "emotional eating," a subdimension of the scale, was one of the factors that caused uncontrolled weight gain. However, emotional eating was found to be less prevalent among the participants. This led us to believe that loss of control over eating and difficulty in focusing on eating might have a greater impact on BMI. At the same time, in this study, we can say that the subdimension of emotional eating was not severe enough to affect the MEQ total. It may be an alternative to evaluate the relationship between BMI and emotional eating using another scale that includes only emotional eating. EM is a skill training and behavior that can be acquired. It is known that EM is low in individuals with obesity,

**Table 4. Correlation of age BMI and scale scores**

| | | Age | BMI | PSQI | NEQ | MEQ total |
|---|---|---|---|---|---|---|
| BMI | r | **0.311** | | | | |
| | p | **0.001** | | | | |
| PSQI | r | -0.089 | **0.170** | | | |
| | p | 0.082 | **0.001** | | | |
| NEQ | r | **-0.112** | **0.149** | **0.737** | | |
| | p | **0.029** | 0.003 | 0.001 | | |
| MEQ total | r | 0.050 | **-0.154** | **-0.213** | **-0.126** | |
| | p | 0.329 | **0.003** | **0.001** | **0.014** | |
| Disinhibition | r | 0.036 | **-0.132** | **-0.182** | **-0.124** | **0.733** |
| | p | 0.489 | **0.010** | **0.001** | **0.016** | **0.001** |
| Emotional eating | r | 0.068 | **-0.159** | **-0.205** | **-0.144** | **0.805** |
| | p | 0.184 | **0.002** | **0.001** | **0.005** | **0.001** |
| Eating control | r | **0.140** | **-0.111** | **-0.277** | **-0.229** | **0.734** |
| | p | **0.006** | **0.030** | **0.001** | **0.001** | **0.001** |
| Focus | r | 0.010 | **-0.109** | **-0.171** | **-0.111** | **0.734** |
| | p | 0.845 | **0.034** | **0.001** | **0.030** | **0.001** |
| Eating discipline | r | -0.020 | -0.090 | -0.095 | -0.040 | **0.663** |
| | p | 0.696 | 0.079 | 0.063 | 0.435 | **0.001** |
| Mindfulness | r | -0.030 | -0.035 | -0.045 | 0.029 | **0.696** |
| | p | 0.562 | 0.497 | 0.382 | 0.569 | **0.001** |
| Interference | r | 0.041 | -0.093 | **-0.162** | -0.094 | **0.716** |
| | p | 0.420 | 0.070 | **0.002** | 0.066 | **0.001** |

BMI: Body mass index, NEQ: Night Eating Questionnaire, PSQI: Pittsburgh Sleep Quality Index, MEQ: Mindful Eating Questionnaire

**Table 5. Linear regression analysis of factors associated with NEQ**

| | β | SE | Standard β | t | p |
|---|---|---|---|---|---|
| **NEQ ($R^2$=0.395; F=28.521; p<0.001)** | | | | | |
| PSQI | 1,169 | 0.082 | 0.595 | 14,278 | **<0.001** |
| Disinhibition | -0.136 | 0.141 | -0.073 | -0.968 | 0.334 |
| Emotional eating | -0.163 | 0.132 | -0.092 | -1,240 | 0.216 |
| Eating control | -0.425 | 0.145 | -0.214 | -2,939 | **0.003** |
| Focus | -0.210 | 0.141 | -0.101 | -1,489 | 0.137 |
| Eating discipline | -0.211 | 0.163 | -0.081 | -1,298 | 0.195 |
| Mindfulness | 0.064 | 0.133 | 0.031 | 0.486 | 0.627 |
| Interference | -0.002 | 0.236 | -0.001 | -0.010 | 0.992 |
| MEQ total | 0.157 | 0.088 | 0.375 | 1,774 | 0.077 |

NEQ: Night Eating Questionnaire, PSQI: Pittsburgh Sleep Quality Index, MEQ: Mindful Eating Questionnaire

and EM can also be observed in people who live with obese people. On the other hand, this study also found that EM was significantly lower in people who had a family member with obesity in their family history. To this end, programs that involve families try to develop EM skills in children to prevent childhood obesity (31).

As participants' night eating behaviors increased, their sleep quality decreased. To the extent that sleep quality decreased, EM (with the exception of eating discipline and mindfulness) also significantly decreased. In other words, as sleep quality decreased, participants' emotional eating decreased, they experienced difficulty restraining themselves from eating, and their control over their timing, speed, and amount of food intake decreased. It became more difficult for them to cope with the distractions of eating. It has been reported that shortening sleep duration can lead to excessive caloric intake by affecting both eating behavior and diet composition. These individuals have been shown to eat more, tend to consume junk food, and choose high-calorie foods. In addition, poor sleep quality disrupts the mechanisms that influence appetite control (32). Another important finding of our study is that sleep quality predicts attitude toward night eating. We know that NES is also related to sleep problems and sleep quality (7). In a 2017 study, individuals with NES symptoms experienced shorter sleep duration and poorer sleep quality than those without NES symptoms. Eating and sleeping rhythms, which are closely linked and synchronized, are disrupted in people diagnosed with NES (33).

While the participants' night eating behaviors increased, their EM decreased. This decrease included less disinhibition of eating, less emotional eating, loss of eating control, and increased preoccupation with thoughts other than eating. The overweight observed in NES was related to eating control (34). Mindfulness means paying attention and observing by focusing on the moment in a controlled manner. When a person with NES eats after waking up, it is not related to mindfulness, although it actually happens at the conscious level (13). Most eating disorder studies have shown that higher levels of mindfulness are associated with lower levels of eating disorder psychopathology (35,36). Another important finding of our study is that "eating control" in EM predicts participants' night eating attitudes. This indicates that individuals with NES generally prefer high-sugar and high-fat foods at night. These individuals lack cognitive and behavioral skills for self-control and exhibit an exaggerated reward response to eating based on the same neural pathways as those with obesity (37).

### Study Limitations

The limitations of this study include its single-center nature and the presence of participants using psychotropic drugs, as well as the potential influence of additional organic diseases on eating and sleep.

## Conclusion

Our findings indicate that NES is under the influence of biopsychological factors associated with psychopathology in psychiatric outpatient clinics. Similarly, NES, EM, and sleep quality were closely related. The fact that participants were overweight in terms of BMI underscores the importance of this relationship. NES predicts "eating control" and sleep quality in the EMQ. Structured and controlled eating patterns with high EM may improve BMI control and sleep quality. Sleep problems in patients with psychiatric disorders should also be investigated in terms of patients' eating attitudes. The eating habits of these patients and their eating attitudes should be carefully examined, and appropriate training should be provided.

**Ethics Committee Approval:** Ethical approval for the study was obtained from the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 56, date: 11.02.2022).

**Informed Consent:** Written informed consent was obtained from all participants.

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## References

1. Kucukgoncu S, Midura M, Tek C. Optimal management of night eating syndrome: challenges and solutions. Neuropsychiatr Dis Treat. 2015; 11: 751-60.
2. Geliebter A. New developments in binge eating disorder and the night eating syndrome. Appetite. 2002; 39: 175-7.
3. Küçükgöncü S, Beştepe E. Night Eating syndrome in major depression and anxiety disorders. Noro Psikiyatr Ars. 2014; 51: 368-75.
4. Elkholy OAE, Molokhia T, Rizk ME. Night eating syndrome among patients with major depressive disorder. Egyptian Journal of Psychiatry. 2023; 44: 82-9.
5. Stunkard A, Berkowitz R, Wadden T, Tanrikut C, Reiss E, Young L. Binge eating disorder and the night eating syndrome. Int J Obes Relat Metab Disord. 1996; 20: 1-6.
6. Allison KC, Goel N. Timing of eating in adults across the weight spectrum: metabolic factors and potential circadian mechanisms. Physiology & behavior. 2018; 192: 158-66.
7. Yoshida J, Eguchi E, Nagaoka K, Ito T, Ogino K. Association of night eating habits with metabolic syndrome and its components: a longitudinal study. BMC Public Health. 2018; 18: 1-12.
8. Lyzwinski LN, Caffery L, Bambling M, Edirippulige S. The mindfulness app trial for weight, weight-related behaviors, and stress in university students: randomized controlled trial. JMIR Mhealth and Uhealth. 2019; 7: e12210.
9. Blac M. Mindful eating for weight loss: try before you buy. The Journal of Clinical Endocrinology & Metabolism 2019; 104: 864-6.
10. Allison KC, Ahima RS, O'Reardon JP, Dinges DF, Sharma V, Cummings DE, et al. Neuroendocrine profiles associated with energy intake, sleep, and stress in the night eating syndrome. J Clin Endocrinol Metab. 2005; 90: 6214-7.
11. Lundgren, JD, Rempfer MV, Brown CE, Goetz J, Hamera E. The prevalence of night eating syndrome and binge eating disorder among overweight and obese individuals with serious mental illness. Psychiatry Research. 2010; 175: 233-6.
12. Elkholy OAE, Molokhia T, Rizk ME. Night eating syndrome among patients with major depressive disorder. Egyptian Journal of Psychiatry. 2023; 44: 82-9.

13. Allison KC, Lundgren JD, O'Reardon JP, Martino NS, Sarwer DB, Wadden TA, et al. The Night Eating Questionnaire (NEQ): psychometric properties of a measure of severity of the Night Eating Syndrome. Eating behaviors. 2008; 9: 62-72.

14. Atasoy N, Saraçlı Ö, Konuk N, Ankarali H, Guriz SO, Akdemir A, et al. The reliability and validity of Turkish version of the Night Eating Questionnaire in psychiatric outpatient population. Anatolian Journal of Psychiatry. 2014; 15: 238-47.

15. Framson C, Kristal AR, Schenk JM, Littman AJ, Zeliadt S, Benitez D. Development and validation of the mindful eating questionnaire. Journal of the American dietetic Association. 2009; 109: 1439-44.

16. Köse G, Tayfur M, Birincioğlu İ, Dönmez A. Adaptation study of the mindful eating questionnare (MEQ) into Turkish. Journal of Cognitive-Behavioral Psychotherapy and Research. 2016; 5: 125-34.

17. Ağargün MY, Kara H, Anlar Ö. The validity and reliability of the Pittsburgh Sleep Quality Index. Turk Psikiyatri Derg. 1996; 7: 107-15.

18. Civil Arslan F, Tiryaki A, Sağlam Aykut D, Özkorumak E, Çalışkan İlter Z, Günaydin D. The prevalence of night eating syndrome among outpatient overweight or obese ındividuals with serious mental Illness. Turkish Journal of Psychiatry. 2015; 26: 242-8.

19. Palmese LB, DeGeorge PC, Ratliff JC, Srihari VH, Wexler BE, Krystal AD, et al. Insomnia is frequent in schizophrenia and associated with night eating and obesity. Schizophrenia research. 2011; 133: 238-43.

20. Saraçlı Ö, Atasoy N, Akdemir A, Güriz O, Konuk N, Sevinçer GM, et al. The prevalence and clinical features of the night eating syndrome in psychiatric out-patient population. Comprehensive psychiatry. 2015; 57: 79-84.

21. Dir AL, Karyadi K, Cyders MA. The uniqueness of negative urgency as a common risk factor for self-harm behaviors, alcohol consumption, and eating problems. Addictive behaviors. 2013; 38: 2158-62.

22. Nazar BP, Bernardes C, Peachey G, Sergeant J, Mattos P, Treasure J. The risk of eating disorders comorbid with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. International Journal of Eating Disorders. 2016; 49: 1045-57.

23. Karataş YF, Müftüoğlu S. Assessment Of mindful eating status of students ın the college of health science. Sağlık Bilimlerinde Eğitim Dergisi. 2020; 3: 24-33 (Turkish).

24. Peuhkuri K, Sihvola N, Korpela R. Diet promotes sleep duration and quality. Nutrition Research. 2012; 32: 309-19.

25. Antunes BM, Campos EZ, Parmezzani SS, Santos RV, Franchini E, Lira FS. Sleep quality and duration are associated with performance in maximal incremental test. Physiology & Behavior. 2017; 177: 252-6.

26. Espel-Huynh HM, Muratore AF, Lowe MR. A narrative review of the construct of hedonic hunger and its measurement by the Power of Food Scale. Obesity Science & Practice. 2018; 4: 238-49.

27. Bruzas MB, Allison KC. A review of the relationship between night eating syndrome and body mass index. Current Obesity Reports. 2019; 8: 145-55.

28. Miller CK. Mindful eating with diabetes. Diabetes Spectrum. 2017; 30: 89-94.

29. Beshara M, Hutchinson AD, Wilson C. Does mindfulness matter? Everyday mindfulness, mindful eating and self-reported serving size of energy dense foods among a sample of South Australian adults. Appetite. 2013; 67: 25-9.

30. Kes D, Can Çicek S. Mindful eating, obesity, and risk of type 2 diabetes in university students: A cross-sectional study. In Nursing Forum. 2021; 56: 483-9.

31. Bozkurt BK, Köksal E. Adaptation of the Mindful Eating Intervention Program for Children and Their Families to Turkish Culture. Bes Diy Derg. 2021; 49: 84-92.

32. Chaput JP. Sleep patterns, diet quality and energy balance. Physiology & Behavior. 2014; 134: 86-91.

33. Yahia N, Brown C, Potter S, Szymanski H, Smith K, Pringle L, et al. Night eating syndrome and its association with weight status, physical activity, eating habits, smoking status, and sleep patterns among college students. Eat Weight Disord. 2017; 22: 421-33.

34. Hays NP, Bathalon GP, McCrory MA, Roubenoff R, Lipman R, Roberts SB. Eating behavior correlates of adult weight gain and obesity in healthy women aged 55-65 y. Am J Clin Nutr. 2002; 75: 476-83.

35. Masuda A, Price M, Latzman RD. Mindfulness moderates the relationship between disordered eating cognitions and disordered eating behaviors in a non-clinical college sample. J Psychopathol Behav Assess. 2012; 34: 107-15.

36. Lavender JM, Gratz KL, Anderson DA. Mindfulness, body image, and drive for muscularity in men. Body Image. 2012; 9: 289-92.

37. Pollack LO, Lundgren JD. Using the neuroscience of obesity, eating behavior, and sleep to ınform the neural mechanisms of night eating syndrome. Curr Obes Rep. 2014; 3: 79-90.

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# Evaluation of the Association between COVID-19 Vaccines and Pulmonary Embolism

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## ABSTRACT

**Introduction:** This study investigated the clinical and radiological characteristics and demographics of patients who developed pulmonary embolism (PE) after Coronavirus disease-2019 (COVID-19) vaccination.

**Methods:** The cases of PE were analyzed retrospectively. Data on clinical, demographic, and radiologic characteristics, laboratory findings, Pulmonary Embolism Severity Index (PESI) scores, early mortality scores, PE severity classes, and risk categories for early mortality (low-risk, intermediate-high-risk, intermediate-low-risk and high-risk) were collected from patient files as defined in the European Society of Cardiology guidelines. Patients were divided into two groups: those who had received a COVID-19 vaccine (group 1) and those who had not (group 2). Patients who developed PE within 1 month after vaccination were analyzed separately.

**Results:** A total of 97 patients were included in the study, of whom 61 (62.9%) patients were female. Seventy-five (77.3%) study patients with PE had a history of COVID-19 vaccination (group 1), and 22 (22.7%) had never been vaccinated (group 2). Five (6.6%) patients had received a vaccine within 1 month before PE developed. No significant differences were found between groups 1 and 2 regarding demographics, clinical and radiologic characteristics, laboratory findings, PESI scores, early mortality scores, and PE severity classes ($p>0.05$), except for mean pulmonary artery pressures. The mean age of patients who developed PE within 1 month after vaccination was 74.6 years, and 80% of these patients were female. The average time to PE after vaccination was 22.2 days, and the mean PESI score was 86.6. Two patients (40%) were in the low-risk category for early mortality and one patient (20%) was in the intermediate/high-risk category.

**Conclusion:** Overall, the characteristics of patients who developed PE after COVID-19 vaccination were comparable to those of patients who had not received a vaccine injection. No statistically significant increases in the incidence of PE were observed within the first month after being vaccinated.

**Keywords:** COVID-19, COVID-19 vaccine, pulmonary embolism

## Introduction

Coronavirus disease-2019 (COVID-19) emerged 4 years ago and was defined as a disease caused by a novel coronavirus strain (2019-nCoV) never previously identified in humans. The disease spread rapidly all over the world and resulted in one of the deadliest pandemics in recent history, mainly transmitted from infected people through droplets generated during activities such as sneezing and coughing. At the beginning of the pandemic, antiviral therapies specific to COVID-19 were not available. In the global pandemic, vaccination is among the most cost-effective ways to fight the disease; therefore, efforts have been made worldwide to develop a vaccine against 2019-nCoV (1,2).

As is well known, vaccine development is a sophisticated process that begins with cell cultures, recombinant DNA technology, and digital modeling to produce strains and antigens to be used in vaccine manufacturing, followed by preclinical studies (phase 0) and clinical trial phases (phase 1, phase 2, and phase 3 clinical trials). As with COVID-19, it may be challenging to develop, perform comprehensive testing, and enable the mass production of effective and, most importantly, reliable vaccines during a pandemic caused by an airborne infection that is rapidly spreading via droplets. Multiple COVID-19 vaccines were developed and approved in a short period and remain in use. However, any vaccine developed and widely administered within a short period should be closely monitored for its effects and possible adverse effects (3-5).

To date, many studies have investigated the effects and adverse effects of COVID-19 vaccines (5-7). Many cases of pulmonary embolism (PE) have been reported in association with COVID-19 vaccination, and studies, mainly consisting of case reports, have suggested a causal relationship

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between COVID-19 vaccination and PE occurring within the first month after vaccination (8,9). This study investigated the clinical, demographic, and radiological characteristics of patients who developed PE after receiving COVID-19 vaccine. Furthermore, subgroup analyses were performed in patients with PE attributed to COVID-19 vaccination who developed PE within the first month after vaccination. The results are reported in light of the literature.

## Methods

This retrospective study was designed by the Ethics Committee of University of Health Sciences Turkey, İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2023/0768, date: 08.11.2023) and was conducted in line with the principles of the Declaration of Helsinki. Consent was obtained from the patients. Hospital files were retrospectively reviewed to identify patients diagnosed with PE based on computed tomography (CT)-angiography of the chest between August 2021 and September 2023 at the Department of Pulmonary Medicine of our hospital. Data on the clinical, demographic, radiological, and laboratory characteristics of patients were collected from the patient files.

**Clinical and demographic characteristics of the study population:** For each study patient, age and sex information, comorbidities, body temperature, pulse, blood pressure, and heart rate at diagnosis, as well as oxygen saturation and arterial blood gas, including partial oxygen saturation ($pO_2$) at hospital admission, were recorded.

### Risk factors for pulmonary embolism

The European Society of Cardiology (ESC) Risk factors for PE were recorded for each patient (10).

Major risk factors for PE include hospitalization for lower extremity fractures, heart failure, or atrial fibrillation (last 3 months), hip or knee replacement surgery, major trauma, history of myocardial infarction in the last 3 months, history of venous thromboembolism (VTE), and spinal cord damage.

Intermediate risk factors for PE include arthroscopic knee surgery, autoimmune diseases, blood transfusions, indwelling central venous catheters and intravenous catheters, chemotherapy, congestive heart failure or respiratory failure, erythropoiesis-stimulating agents, hormone replacement therapy, in vitro fertilization, oral contraceptives, postpartum therapy, infections (pneumonia, urinary tract infection and HIV, in particular), inflammatory bowel disease, cancers (higher risk in the presence of metastases), stroke, superficial vein thrombosis, and thrombophilia.

Low-risk factors for PE include bed rest for more than 3 days, diabetes mellitus, elevated arterial blood pressure, prolonged static sitting, advanced age, laparoscopic surgery, obesity, pregnancy, varicose veins, and indwelling venous catheters.

**Imaging characteristics of the population:** Chest CT angiography findings including the bilateral distribution of thrombi within the pulmonary arterial system, in the root of the pulmonary trunk, lobar, segmental, and subsegmental branches, and any PE-associated infiltrations or pleural effusions were noted. If present, signs of right ventricular strain and pulmonary artery systolic pressure on echocardiogram (ECHO) and any thrombus images on Doppler ultrasound (US) were noted.

**Laboratory features of the population:** Results from routine laboratory tests, including complete blood counts, white blood cell counts, platelet (PLT) counts, mean platelet volume, C-reactive protein, procalcitonin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, urea and creatinine, electrolytes, troponin, brain natriuretic peptide, D-dimer measurements at diagnosis, and on treatment were reviewed and noted.

**Prognostic and early mortality evaluations:** The ESC prognostic scores for early mortality were recorded for each patient (10). The Pulmonary Embolism Severity Index (PESI) score was used for the prognostic assessment of PE. According to the guidelines of the ESC, patients were classified as having a low-risk for early mortality in PESI scoring class I and II and high risk for early mortality in PESI scoring class III and above (class III-IV-V) (Supplementary Table 1) (10).

The study patients were classified into low-, intermediate-low-, intermediate-high-, and high-risk groups according to the Classification of Pulmonary Embolism Severity and the risk of early (in-hospital or 30-day) death (Supplementary Table 2). Hemodynamic instability in PE was defined as cardiac arrest, obstructive shock, and persistent hypotension according to the ESC guidelines (Supplementary Table 3) (10).

PESI scores and the numbers of patients in the low-, intermediate-low-, intermediate-high-, intermediate-low-, and high-risk groups for early mortality and, if present, hemodynamic instability were also recorded.

Study patients were divided into two groups based on the presence (group 1) or absence (group 2) of a history of having received any COVID-19 vaccine before the occurrence of PE, and intergroup comparisons were performed. Furthermore, all aforementioned characteristics were documented and analyzed in the subgroup of cases of PE assumed to be related to the vaccine.

The exclusion criteria were uncertainty in the diagnosis of PE or COVID-19, diagnosis of PE using methods other than CT angiography of the chest [e.g. based on ventilation-perfusion (V/Q) scintigraphy, and/or clinical diagnosis], pregnancy, and age under 18 years.

### Statistical Analysis

All data were analyzed using SPSS 17.0 software (IBM Inc. Released in 2008. SPSS Statistics for Windows (Chicago, USA). In descriptive statistics, normally distributed continuous variables are presented as means ± standard deviation, and categorical variables are presented as percentages. The Kolmogorov-Smirnov test was used to determine whether the variables were normally distributed. The chi-square and Mann-Whitney U tests were used for intergroup comparisons of data. A p-value of less than 0.05 was considered significant.

## Results

In total, 130 patient files were reviewed for eligibility. Out of the 130 patients, 30 were excluded because their vaccination status was unknown, two were excluded because of uncertainty regarding the diagnosis of COVID-19, and one was excluded because the diagnosis of PE was made based on V/Q scintigraphy (Figure 1).

The mean age of the overall study patients was 67.7±18 years, a total of 97 patients, including 61 (62.9%) females and 36 (37.1%) males were found to be eligible for the study. Seventy-five study patients had a history of COVID-19 vaccination before the diagnosis of PE (group 1), whereas 22 study patients (22.7%) had not (group 2). The mean time to the diagnosis of PE after getting vaccinated against COVID-19 was 227.3±157.7 days (minimum-maximum: 9 days and 793 days, respectively) in group 1. Five (6.6%) study patients were diagnosed with PE within 1 month after being vaccinated, and eight (10.6%) study patients were diagnosed with PE at month 2 after being vaccinated (Figure 2). Fifty-two patients received nucleic acid vaccines-COVID-19 vaccines (mRNA) and 23 patients (30.7%) received inactivated vaccines.

Regarding the risk factors for PE, 47 (62.7%) patients in group 1 and 14 (63.7%) patients in group 2 had one risk factor for developing PE (p=0.934). Thirty-four (45.3%) patients in group 1 and six (27.2%) patients in group 2 had major or intermediate risk factors (0.130). Eleven patients in group 1 (14.6%) and eight patients (36.6%) had a low-risk factor (0.034) (Table 1).

Seventy-three (75.3%) patients had a comorbidity and 24 patients (24.7%) did not. Hypertension (HTN) was the most common comorbidity in 37 patients. The mean length of hospital stay was 9.47±5.65 days [9.45±5.2 days in groups 1 and 9.55±6.9 days in group 2 (p=0.431)]. The clinical and demographic characteristics of the study patients are presented in Table 2, and the laboratory test results are presented in Table 3. Based on echocardiographic measurements, the PABs were 46.1±11.5 in patients who had received a COVID-19 vaccination and 38.3±15.9 in those who had not (p=0.022). No other intergroup statistically significant differences were found in other radiologic variables. Data from comprehensive imaging studies (CT-angiography of the chest, ECHO, bilateral lower extremity venous Doppler US) are presented in Table 4.

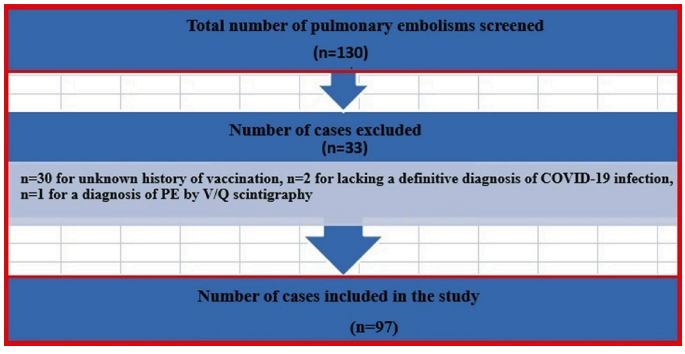


**Figure 1.** Flow chart
COVID-19: Coronavirus disease-2019, PE: Pulmonary embolism

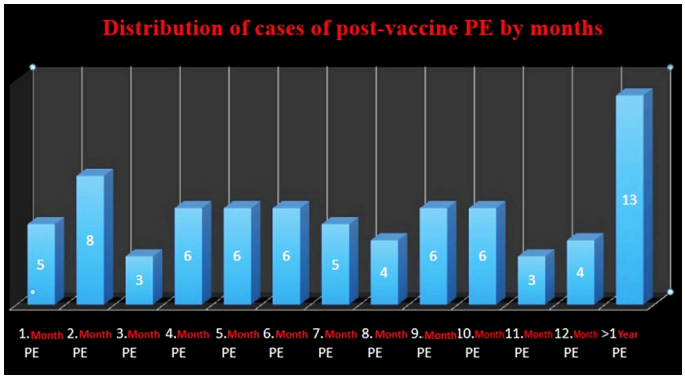


**Figure 2.** Distribution of cases of post-vaccine PE according to months
PE: Pulmonary embolism

**Table 1. Distribution of study patients according to risk factors**

| | COVID-19 vaccinated (group 1; n=75) | COVID-19 unvaccinated (group 2; n=22) | p-value |
|---|---|---|---|
| Major risk factors (n, %) | 22-29.3% | 3-13.6% | 0.139 |
| Intermediate-risk factors (n, %) | 12-16% | 3-13.6% | 1 |
| Low-risk factors (n, %) | 11-14.6% | 8-36.3% | **0.034** |
| Inherited risk factors (n, %) | 2-2.6% | - | 1 |
| No risk factors (n, %) | 28-37.3% | 8-36.3% | 0.934 |

COVID-19: Coronavirus disease-2019

**Table 2. Patient demographics and clinical characteristics of patients**

| | COVID-19 vaccinated (group 1; n=75) | COVID-19 unvaccinated (group 2; n=22) | p-value |
|---|---|---|---|
| Age (mean ± SD) | 66.5±18.4 | 71.7±16.3 | 0.199 |
| Sex (F/M; n, %) | 47-62.6/28-37.4% | 14-63.6/8-36.3% | 0.934 |
| Hospital stay (days, mean ± SD) | 9.45±5.2 | 9.55±6.9 | 0.431 |
| **Comorbidities** | | | |
| - Any comorbidity (n, %) | 56-74.6% | 17-77.2% | 0.803 |
| - Hypertension (n, %) | 30-40% | 7-31.8% | 0.487 |
| - Malignancy | 16-21.3% | 2-9% | 0.348 |
| - DM (n, %) | 16-21.3% | 5-22.7% | 1 |
| - CAD (n, %) | 9-12% | 2-9% | 1 |
| - CHF (n, %) | 6-8% | 2-9% | 1 |
| - COPD (n, %) | 9-12% | 2-9% | 1 |
| - Asthma (n, %) | 4-5.3% | 1-4.5% | 1 |
| - CVA (n, %) | 7-9.3% | 2-9% | 1 |
| - CKF (n, %) | 2-2.6% | 0- | 1 |
| Body temperature (mean ± SD) (°C) | 36.5±0.2 | 36.4±0.1 | 0.222 |
| Heart rate (mean ± SD) (/minute) | 94.7±19 | 95.9±21 | 0.919 |
| Systolic blood pressure (mean ± SD) (mmHg) | 127.6±26.1 | 116.3±21.4 | 0.095 |
| Diastolic blood pressure (mean ± SD) (mmHg) | 74.6±12.7 | 68±13.1 | 0.070 |
| Admission oxygen saturation (%) | 90.3±4.5 | 91.7±4.2 | 0.197 |
| ABG-$pO^2$ (mmHg) (mean ± SD) | 60.3±13.2 | 63.5±14.5 | 0.274 |

ABG: Arterial blood gas, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, CAD: Coronary arterial disease, CKF: Chronic kidney failure, mmHg: millimeter mercury, $pO_2$: Partial oxygen pressure, SD: Standard deviation, CVA: Cerebrovascular accident

The mean PESI score was 99.9±33.5 in group 1 and 104±38.9 in group 2 (p=0.763). Fifty-one patients (68%) in group 1 were classified as PESI-III or higher, and 13 patients (59%) were classified as PESI-III or higher in group 2 (p=0.438) (Table 5). The assessment of the risk of early death revealed that 10 patients (13.3%) in group 1 and two patients (9%) in group 2 were at high risk of early mortality (p=0.729). Nine (12%) patients and two (9%) patients presented with hemodynamic instability in groups 1 and 2, respectively (p=1). No statistically significant intergroup differences were observed regarding prognostic status and early mortality scores (Table 6).

**Subgroup analyses of PE cases attributable to vaccination:** Five patients in group 1 were diagnosed with PE within 1 month after being vaccinated against COVID-19. The mean age of these patients was 74.6±19.4 (minimum: 43, maximum: 92) years, and four (80%) patients were women. The mean time interval between getting vaccinated and PE onset was 22.2±10.1 (minimum: 9, maximum: 31) days. Among these patients, two (40%) received an inactive vaccine and three (60%) received an mRNA vaccine before developing PE. No risk factors were detected in three patients (60%); one patient (20%) had a low-risk factor, and one patient (20%) had an inherited risk factor for PE. Comorbidities were identified in four patients (80%), and one patient (20%) had no comorbidities. The most prevalent comorbidity was HTN (n=3, 60%). The mean length of hospital stay was 5.6±0.8 (minimum: 5, maximum: 7) days. The mean PLT count was 273,400±142,449 (minimum: 126,000, maximum: 440,000). Imaging studies revealed that PE mostly affected the bilateral subsegmental branches of pulmonary arteries (three patients, 60%) (Table 7). The mean PESI score was 86.6±16.7.

**Table 3. Laboratory characteristics**

| | COVID-19 vaccinated (group 1; n=75) | COVID-19 unvaccinated (group 2; n=22) | p-value |
|---|---|---|---|
| Laboratory parameters | | | |
| WBC (mean ± SD) (/uL) | 10,934±4,203 | 8,981±3,432 | 0.189 |
| Hb (mean ± SD) (g/dL) | 12.1±2 | 12.1±2.1 | 0.911 |
| PLT (mean ± SD) (/uL) | 244,733±88,415 | 278,272±124,129 | 0.268 |
| MPV (mean ± SD) (/uL) | 10.8±1.4 | 10.2±0.9 | 0.245 |
| LDH (mean ± SD) (U/L) | 285.8±174.9 | 236.7±127.5 | 0.338 |
| D-dimer level (mean ± SD) (mg/L) | 10.5±9.8 | 12±10.9 | 0.619 |
| Urea (mean ± SD) (mg/dL) | 50.3±58.1 | 40.2±12.1 | 0.850 |
| Creatinine (mean ± SD) (mg/dL) | 1±0.5 | 0.77±0.2 | 0.011 |
| ALT (mean ± SD) (U/L) | 31.4±39 | 21.2±20.2 | 0.110 |
| AST (mean ± SD) (U/L) | 34.7±39.5 | 24.8±17.8 | 0.144 |
| Albumin (mean ± SD) (g/L) | 36.5±5.9 | 36±6.5 | 0.945 |
| BNP (mean ± SD) (ng/L) | 3674±6044 | 4119±4809 | 0.336 |
| Troponin (mean ± SD) (ng/L) | 77±145.8 | 77.3±144.4 | 0.181 |

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BNP: Brain natriuretic peptide, CRP: C-reactive protein, HB: Hemoglobin, LDH: Lactate dehydrogenase, MPV: Mean platelet volume, PLT: Platelet, PRC: Procalcitonin, SD: Standard deviation, WBC: White blood cell

**Table 4. Imaging and echocardiographic characteristics**

| | COVID-19 vaccinated (group 1; n=75) | COVID-19 unvaccinated (group 2; n=22) | p-value |
|---|---|---|---|
| Embolism in the main pulmonary artery (n, %) | 1-1.3% | 0 | 1 |
| Embolism in the left pulmonary artery (n, %) | 11-14.6% | 5-22.7% | 0.350 |
| Embolism in the right pulmonary artery (n, %) | 4-5.3% | 2-9% | 0.616 |
| Embolism in both pulmonary arteries (n, %) | 18-24% | 6-27.2% | 0.754 |
| Embolism in unilateral segmental branches (n, %) | 26-34.6% | 2-9% | 0.020 |
| Embolism in bilateral segmental branches (n, %) | 40-53.3% | 13-59% | 0.613 |
| Embolism in unilateral subsegmental branches (n, %) | 23-30.6% | 2-9% | 0.042 |
| Embolism in bilateral subsegmental branches (n, %) | 41-54.6% | 12-54.5% | 0.992 |
| Pleural effusion associated with pulmonary embolism (n, %) | 17-22.6% | 9-40.9% | 0.089 |
| Parenchymal infarct area (n, %) | 37-49.3% | 11-50% | 0.956 |
| Thrombus on Doppler US (n, %) | 18-24% | 8-36.3% | 0.250 |
| Right ventricular involvement in ECHO (n, %) | 28-37.3% | 12-54.5% | 0.149 |
| PAP value on ECHO (mean ± SD) (mmHg) | 38.3±15.9 | 46.1±11.5 | 0.022 |

ECHO: Echocardiogram, PAPs: Systolic pulmonary arterial pressure, mmHg: Millimeter mercury, US: Ultrasound, COVID-19: Coronavirus disease-2019

**Table 5. Patient distribution according to PESI scores**

| | COVID-19 vaccinated (group 1; n=75) | COVID-19 unvaccinated (group 2; n=22) | p-value |
|---|---|---|---|
| PESI-I (n, %) | 11-15.3% | 2-12.6% | 0.726 |
| PESI-II (n, %) | 13-17.3% | 7-26.2% | 0.147 |
| PESI-III (n, %) | 19-26.9% | 3-24.2% | 0.386 |
| PESI-IV (n, %) | 18-30.7% | 3-21.3% | 0.387 |
| PESI-V (n, %) | 14-26.9% | 7-15.5% | 0.239 |

PESI: Pulmonary Embolism Severity Index, COVID-19: Coronavirus disease-2019

**Tablo 6. Patient distribution by EMA**

| | COVID-19 vaccinated (group 1; n=75) | COVID-19 unvaccinated (group 2; n=22) | p-value |
|---|---|---|---|
| High | 10-13.3% | 2-9% | 0.729 |
| Intermediate-high | 15-20% | 2-9% | 0.344 |
| Intermediate-low | 26-34.6% | 7-31.8% | 0.804 |
| Low | 24-32% | 11-50% | 0.122 |

EMA: Early mortality assessment [classification of pulmonary embolism severity and the risk of early death (in-hospital or 30-day)]

**Table 7. Demographics, clinical, laboratory, and radiological characteristics of patients with PE attributable to vaccine**

| | Patients who developed PE within the first month after receiving COVID-19 vaccine (n=5) |
|---|---|
| Age (mean ± SD) | 74.6±19.4 |
| Sex (F/M; n, %) | 4-8/1-20% |
| **Comorbidities** | |
| - Hypertension (n, %) | 3-60% |
| - CAD (n, %) | 1-20% |
| - COPD (n, %) | 1-20% |
| - Hypothyroidism (n, %) | 1-20% |
| **Klinik parametreler** | |
| - Body temperature (mean ± SD) | 36.4±0.22 |
| - Heart rate (mean ± SD) | 101±20.7 |
| - Systolic blood pressure (mean ± SD) | 119±7.4 |
| - Diastolic blood pressure (mean ± SD) | 71.6±13.5 |
| - Admission oxygen saturation (mean, %) | 91.8±2.8 |
| - ABG-$pO_2$ (mmHg) (mean ± SD) | 58±3.2 |
| **Laboratory parameters** | |
| - WBC (mean ± SD) (/uL) | 10,880±7,143 |
| - Hb (mean ± SD) (g/dL) | 13.2±2.2 |
| - PLT (mean ± SD) (/uL) | 273,400±142,449 |
| - LDH (mean ± SD) (U/L) | 257.4±148.7 |
| - D-Dimer level (mean ± SD) (mg/L) | 12.9±13.2 |
| - Urea (mean ± SD) (mg/dL) | 44.2±15.2 |
| - Creatinine (mean ± SD) (mg/dL) | 0.94±0.48 |
| - BNP (mean ± SD) (ng/L) | 379±298.9 |
| - Troponin (mean ± SD) (ng/L) | 45.7±57.5 |
| **Imaging parameters** | |
| - Embolism in the left pulmonary artery (n, %) | 1-20% |
| - Embolism in the right pulmonary artery (n, %) | 1-20% |
| - Embolism in both pulmonary arteries (n, %) | 1-20% |
| - Embolism in unilateral segmental branches (n, %) | 2-40% |
| - Embolism in bilateral segmental branches (n, %) | 2-40% |
| - Embolism in unilateral subsegmental branches (n, %) | 2-40% |
| - Embolism in bilateral subsegmental branches (n, %) | 3-60% |
| - Pleural effusion associated with pulmonary embolism (n, %) | 2-40% |
| - Parenchymal infarct area (n, %) | 2-40% |
| - Thrombus on Doppler US (n, %) | 2-40% |
| - Right ventricular involvement in ECHO (n, %) | 2-40% |
| - PAP value on ECHO (mean ± SD) (mmHg) | 51.6±23.6 |

ABG: Arterial blood gas, BNP: Brain natriuretic peptide, ECHO, Echocardiogram, Hb, hemoglobin, COPD: Chronic obstructive pulmonary disease, CAD: Coronary arterial disease, LDH: Lactate dehydrogenase, mmHg: Millimeter mercury, PAPs: Systolic pulmonary arterial pressure, $pO_2$: Partial oxygen pressure, SD: Standard deviation, US: Ultrasound, WBC: White Blood Cell

One patient was classified into PESI class 1, one patient was classified into PESI class II, two patients were classified into PESI class III, and one patient was classified into PESI class IV, indicating that the PESI class was III or higher in three (60%) patients. Two (40%) patients were at low-risk, two patients (40%) were in the intermediate-low-risk group, and one patient (20%) was classified into the intermediate/high-risk group. No patients were hemodynamically unstable.

## Discussion

This study investigated the features of patients diagnosed with PE after being vaccinated against COVID-19. The rate of patients with PE within 1 month after being vaccinated was 6.6% in the overall study population. No significant differences were found between the group of patients who received COVID-19 vaccine before being diagnosed with PE and the group of patients who did not have clinical, radiological, or laboratory characteristics. The assessment of the presence of risk factors for PE revealed no intergroup differences in risk factors (p=0.934). As an interesting finding, low-risk factors were significantly less prevalent in group 1 (p=0.034).

At the time of writing this article, the total number of COVID-19 vaccine doses administered was 152 million in our country and approximately 1.5 billion in Europe (11,12). The COVID-19 pandemic has accelerated efforts to develop vaccines and build an extensive vaccination program worldwide. Upon the initiation of vaccination programs, several adverse effects have been reported in association with these rapidly developed and widely used vaccines. Increased incidences of thrombotic events, including DIC, cerebral venous sinus thrombosis, hemorrhagic stroke, and PE, were reported from a study in a population of 5.5 million individuals, particularly those vaccinated with ChAdOx1 nCoV-19, AZD1222, a recombinant adenovirus vaccine encoding the SARS-CoV-2 spike glycoprotein. These events predominantly occurred in women aged 60 years, and thrombocytopenia was documented in most thrombotic events. These patients usually deteriorate 6-12 days after being vaccinated (13,14). Increased risk for PE (out of 54,571 adverse events, there were 28 cases of PE and four deaths) after AZD1222 vaccination, and the decision for temporary suspension of the use of the vaccine suggested an association between this vaccine and PE (15).

In one of the limited retrospective studies on this association, Scully et al. (16) analyzed data from 23 patients who presented with thrombosis and thrombocytopenia 6-24 days after receiving COVID-19 vaccine injection. In their study, five out of 23 patients were diagnosed with PE, and 22 tested positive for platelet factor 4. The mean age was 44 years, 60% of the patients were female, and the mean PLT count was 43,200. In our study, the mean age was 66 years in the post-vaccine PE group (62% were female, and the mean PLT count was 244,733. Among those diagnosed with PE within 1 month (5 patients), the mean age was 74.6 years, 80% were female, and the mean PLT count was 273,400 after vaccination. Our results were not consistent with the literature regarding patient characteristics, except for sex.

In the literature, cases of post-vaccine PE are usually reported as case reports. An analysis of 10 recently published cases indicated that the mean patient age was 57 years, 80% were male, and all patients developed PE after receiving a live vaccine injection (100%). The mean

PESI score was 94.5 (minimum: 41, maximum: 129), and the distribution of patients according to the PESI classes was as follows: PESI class 1, 20%; PESI class 2, 10%; PESI class 3, 30%; PESI class 4, 20%; and PESI class 5, 20%. Twenty percent of patients were at high risk, 20% were intermediate high risk, 30% were intermediate-low-risk, and 30% were low-risk for early mortality (9,17-25) (Figure 3). In our study, the mean age was 74 years, and 80% of the patients were female in the group of patients who developed PE after being vaccinated. Sixty percent of patients received a live mRNA vaccine. The mean PESI score was 104, and 15.3% were classified as PESI class 1, 17.3% were PESI class 2, 26.9% were PESI class 3, 39.7% were PESI class 4, and 26.9% were classified as PESI class 5. By contrast, for the early mortality assessment, 13.3% of patients were at high risk, 20% were intermediate high, 34.6% were intermediate/low-risk, and 32% were at low-risk (Figure 4).

Recently, adverse effects associated with COVID-19 mRNA vaccines were investigated by Yasmin et al. (26) in a meta-analysis that included a total of 81 articles and 17,636 patients, and the most common adverse effects were thrombosis (n=3936), CVH (n=758), myocarditis (n=511), myocardial infarction (n=377), PE (n=301), and arrhythmias (n=254). Although PE is a relatively uncommon complication, the authors stated that PE might increase mortality along with myocarditis. Similarly, Favas et al. (27) conducted a meta-analysis that included 59 articles, 202 patients, and 306 events to investigate post-vaccine thrombotic and thromboembolic complications. They reported that 74.8% of patients experienced VTE events, 12.7% developed arterial thromboembolic events, and the remaining developed hemorrhagic complications. PE was reported in 17.8%. The mean patient age was 47 years, 71% of patients were female, the time to event was 14 days (minimum: 1 day and maximum: 37 days), and almost all vaccines associated with events were live/mRNA vaccines. Our study was in line with the literature based on these results. Finally, Wong et al. (28) investigated vaccine safety in patients aged ≥65 years who received 17 million doses and detected remarkable increases in the incidences of PE, myocardial infarction, disseminated intravascular coagulopathy, and immune thrombocytopenia, although only PE was statistically significantly associated with COVID-19 vaccination after the adjustments. The largest amount of information about COVID-19 vaccines and PE available in the English medical literature is from studies involving live/mRNA vaccines. In a postmortem study involving inactive vaccines, Chaves et al. (29) found that 118 out of 121 (97.52%) deceased patients had been vaccinated with an inactive vaccine, and PE was the second most common cause of death (n=25, 20.66%) after sudden cardiac death. In our study, 30% of patients experiencing post-vaccine PE received an inactive vaccine. Inactive vaccines accounted for 40% of the to date, studies and case reports have mostly underlined the hypothesis that COVID-19 vaccines might increase the incidence of PE. However, Tantillo et al. (30) made a very different assumption that had never been investigated before; they investigated whether COVID-19 vaccines could prevent PE. Surprisingly, they found that PE was significantly more prevalent among patients who had NOT received a COVID-19 vaccine. The authors further explained their assumptions using citations from a study conducted by Agrati et al. (31): "We can just hypothesize a possible protective role of vaccination through action on the immune system, modulating the inflammation-coagulation interface".

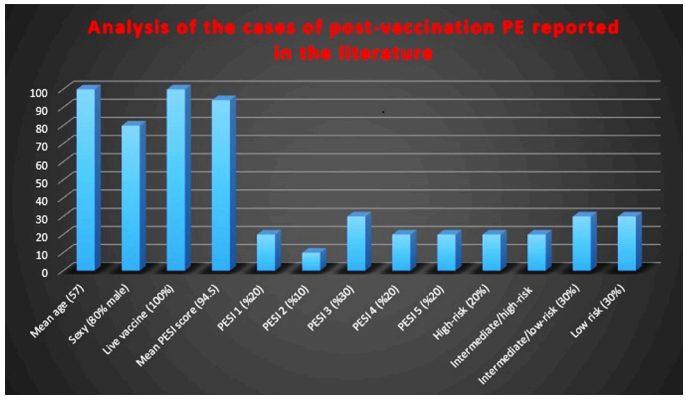


**Figure 3.** Analysis of postvaccination PE cases reported in the literature
PE: Pulmonary embolism, PESI: Pulmonary Embolism Severity Index

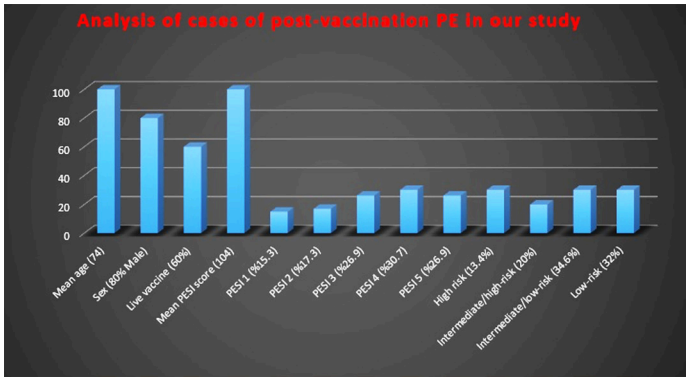


**Figure 4.** Analysis of postvaccination PE cases in our study
PE: Pulmonary embolism, PESI: Pulmonary Embolism Severity Index

### Study Limitations

The present study has some limitations that should be considered when interpreting the results. This study has a retrospective design and reflects a single-site experience. Therefore, the results cannot be generalized. Furthermore, the small sample size, particularly the very limited number of PE cases attributed to vaccines, did not provide sufficient power for statistical analysis. The limited number of cases can be explained by the relatively low incidence of PE. Future studies should have a multicenter design to overcome this limitation.

Many studies have demonstrated several adverse effects associated with COVID-19 vaccination. Moreover, the speed of the development of COVID-19 vaccines has been the primary concern in these studies (32). Therefore, healthcare professionals from branches/disciplines involved in COVID-19 should enhance their knowledge and better manage the effects and adverse effects of vaccines.

## Conclusion

In conclusion, the present study analyzed cases of PE after COVID-19 vaccination. Regarding vaccine complications reported in the medical literature, PE was a relatively less common complication in most studies. However, several studies have suggested that COVID-19 vaccines might decrease the incidence of PE. The parameters analyzed in our study and the results are not sufficient to achieve definitive conclusions on whether COVID-19 vaccines increase or decrease the incidence of PE;

however, considering the number of cases of PE during the first 12 months after vaccination, the cases were not significantly clustered nor did they increase in the first month [month 1, (n=5); month 2, (n=8); month 3, (n=3); month 4, month 5, (n=6); month 6, (n=6) cases (Figure 2)]. Independent of the results, we believe that the potential benefits of COVID-19 vaccines outweigh the potential risks of a COVID-19 infection.

**Ethics Committee Approval:** This retrospective study was designed by the Ethics Committee of University of Health Sciences Turkey, İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2023/0768, date: 08.11.2023) and was conducted in line with the principles of the Declaration of Helsinki.

**Informed Consent:** Consent was obtained from the patients.

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

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

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## References

1. Zhu N, Zhang D, Wang W, Li XX, Yang B, Song J, et al. A Novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382: 727-33.
2. Altmann DM, Boyton RJ. COVID-19 vaccination: The road ahead. Science. 2022; 375: 1127-32.
3. Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020; 19: 305-6.
4. Rémy V, Largeron N, Quilici S, Carroll S. The economic value of vaccination: why prevention is wealth. J Mark Access Health Policy. 2015; 3.
5. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 2020; 586: 589-93.
6. Sheikh A, McMenamin J, Taylor B, Robertson C. Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021; 397: 2461-62.
7. Kadali RAK, Janagama R, Peruru S, Malayala SV. Side effects of BNT162b2 mRNA COVID-19 vaccine: A randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. Int J Infect Dis. 2021; 106: 376-81.
8. Mahgoub AE, Awuah D, Hussain M, Deliwala S, Bachuwa G, Younas M. Development of venous thromboembolism after COVID-19 mRNA-1273 Vaccine Inoculation. Cureus. 2022; 14: e22179.
9. Al-Maqbali JS, Al Rasbi S, Kashoub MS, Al Hinaai AM, Farhan H, Al Rawahi B, et al. 59-year-old woman with extensive deep vein thrombosis and pulmonary thromboembolism 7 days following a first dose of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 Vaccine. Am J Case Rep. 2021; 22: e932946.
10. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020; 41: 543-603.
11. Türkiye Cumhuriyeti Sağlık Bakanlığı COVID-19 Aşısı Bilgilendirme Platformu. Accessed October 30, 2023. https://covid19asi.saglik.gov.tr/
12. European Commission. Accessed 30 October 30, 2023. https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/safe-covid-19-vaccines-europeans_en#figures-on-vaccination
13. Kantarcioglu B, Iqbal O, Walenga JM, Lewis B, Lewis J, Carter CA, et al. An Update on the Pathogenesis of COVID-19 and the Reportedly Rare Thrombotic Events Following Vaccination. Clin Appl Thromb Hemost. 2021; 27: 10760296211021498.
14. European Medicines Agency. Signal assessment report on embolic and thrombotic events with covid-19 vaccine (ChAdOx1-S [recombinant]): Covid-19 vaccine AstraZeneca (other viral vaccines). Accessed March 24, 2021. www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant-covid_en.pdf
15. Tobaiqy M, Elkout H, MacLure K. Analysis of thrombotic adverse reactions of COVID-19 AstraZeneca vaccine reported to eudravigilance database. Vaccines (Basel). 2021; 9: 393.
16. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med. 2021; 384: 2202-11.
17. Kim E-J, Yoo S-J. Pulmonary embolism after vaccination with the COVID-19 Vaccine (Pfizer, BNT162b2): a case report. Vaccines. 2023; 11: 1075.
18. Ogunkoya JO, Ogunmola MI, Ogunlade AF, Ladele AE. COVID-19 Vaccination associated bilateral pulmonary embolism: cause or coincidence. Case Rep Pulmonol. 2022; 2022: 9596285.
19. Miri C, Bouchlarhem A, Boulouiz S, El Ouafi N, Bazid Z. Pulmonary embolism with junctional tachycardia: a serious complication after COVID-19 vaccination. Ann Med Surg (Lond). 2022; 80: 103983.
20. Tews HC, Driendl SM, Kandulski M, Buechler C, Heiss P, Stöckert P, et al. SARS-CoV-2 vaccine-ınduced ımmune thrombotic thrombocytopenia with venous thrombosis, pulmonary embolism, and adrenal haemorrhage: a case report with literature review. Vaccines (Basel). 2022; 10: 595.
21. Borisoff BD, Bohn KD, Sager J, Gracious BL. Unprovoked submassive saddle pulmonary embolism in an adult male after Pfizer COVID-19 vaccination. Cureus. 2022; 14: e27717.
22. Bocchino M, Rea G, Buonocore A, Lieto R, Mazzocca A, Di Domenico A, et al. Combination of acute exacerbation of idiopathic nonspecific interstitial pneumonia and pulmonary embolism after booster anti-COVID-19 vaccination. Respir Med Case Rep. 2022; 38: 101674.
23. Cheong KI, Chen CF, Chen JS, Wu YW, Chiu KM, Tu CM. Acute pulmonary embolism following moderna mRNA-1273 SARS-CoV-2 vaccination - a case report and literature review. Acta Cardiol Sin. 2022; 38: 539-41.
24. Ihnatko M, Truchla I, Ihnatková L, Prohászka Z, Lazúrová I. Case report: a case of COVID vaccine-ınduced thrombotic thrombocytopenia manifested as pulmonary embolism and hemorrhagia. A First Reported Case From Slovakia. Front Med (Lausanne). 2022; 8: 789972.
25. Ifeanyi N, Chinenye N, Oladiran O, David E, Mmonu C, Ogbonna-Nwosu C. Isolated pulmonary embolism following COVID vaccination: 2 case reports and a review of post-acute pulmonary embolism complications and follow-up. J Community Hosp Intern Med Perspect. 2021; 11: 877-9.
26. Yasmin F, Najeeb H, Naeem U, Moeed A, Atif AR, Asghar MS, et al. Adverse events following COVID-19 mRNA vaccines: A systematic review of cardiovascular complication, thrombosis, and thrombocytopenia. Immun Inflamm Dis. 2023; 11: e807.
27. Favas TT, Lall N, Joshi D, Singh VK, Pathak A, Chakravarty K, et al. Thrombotic and thromboembolic complications after vaccination against COVID-19: a systematic review. Cureus. 2023; 15: e37275.

28. Wong HL, Tworkoski E, Ke Zhou C, Hu M, Thompson D, Lufkin B, et al. Surveillance of COVID-19 vaccine safety among elderly persons aged 65 years and older. Vaccine. 2023; 41: 532-9.

29. Chaves JJ, Bonilla JC, Chaves-Cabezas V, Castro A, Polo JF, Mendoza O, et al. A postmortem study of patients vaccinated for SARS-CoV-2 in Colombia. Rev Esp Patol. 2023; 56: 4-9.

30. Tantillo S, Cilloni N, Guarnera M, Talarico F, Citino M, Silingardi M, et al. Does COVID-19 vaccination protect against pulmonary embolism? J Anesth Analg Crit Care. 2023: 30; 3:14.

31. Agrati C, Carsetti R, Bordoni V, Sacchi A, Quintarelli C, Locatelli F, et al. The immune response as a double-edged sword: the lesson learnt during the COVID-19 pandemic. Immunology. 2022; 167: 287-302.

32. Dror AA, Eisenbach N, Taiber S, Morozov NG, Mizrachi M, Zigron A, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. Eur J Epidemiol. 2020; 35: 775-9.

**Supplementary Table 1. PESI scoring scores**

| Variable | PESI | |
|---|---|---|
| >80 years of age | Age/years | |
| Male sex | +10 points | |
| History of cancer | +30 points | |
| History of heart failure | +10 points | |
| History of chronic lung disease | +10 points | |
| Heart rate ≥110/bpm | +20 points | |
| Systolic blood pressure <100 mm Hg | +30 points | |
| Respiratory rate ≥30/minute | +20 points | |
| Body temperature <36 °C | +20 points | |
| Altered mental health | +60 points | |
| $SpO_2$ <90% | +20 points | |
| | **Low-risk**<br>Class I: ≤65<br>Class II: 66-85 | **High-risk**<br>Class III: 86-105<br>Class IV: 106-125<br>Class V: >125 |

PESI: Pulmonary Embolism Severity Index

**Supplementary Table 2. Classification of pulmonary embolism severity and the risk of early death**

| | | Risk indicators | | |
|---|---|---|---|---|
| **Early mortality risk** | **Hemodynamic instability** | **PESI class III-IV** | **Ventricular dysfunction on TTE or computed tomography angiography** | **Increased cardiac troponin levels** |
| High | + | + | + | + |
| Intermediate-high | - | + | + | + |
| Intermediate-low | - | + | One (+) or both (-) | |
| Low | - | - | - | - |

PESI: Pulmonary Embolism Severity Index, TTE: Transthoracic echocardiography

**Supplementary Table 3. Definition of hemodynamic instability in pulmonary embolism**

| Cardiac arrest | Obstructive shock | Persistent hypotension |
|---|---|---|
| Cardiac arrest necessitates cardiopulmonary resuscitation | Systolic blood pressure of <90 mmHg<br>or<br>Need for a vasopressor to maintain systolic blood pressure at ≥90 mmHg despite adequate fluid replacement<br>and<br>End organ hypoperfusion (altered mental status, cold and clammy skin, oliguria/anuria, increased serum lactate levels) | Systolic blood pressure of <90 mmHg<br>or<br>Systolic blood pressure decrease of more than 40 mmHg<br>(New-onset arrythmia lasting longer than 15 minutes, that cannot be explained by hypovolemia or sepsis) |

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# Morphometric Analysis of the Posterior Fossa and Cervical Spinal Canal in Type 1 Chiari Malformation and Its Effects on Syringomyelia Development

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## ABSTRACT

**Introduction:** Chiari malformation (CIM) is a congenital anomaly characterized by herniation of hindbrain structures through the foramen magnum into the cervical spinal canal (CSC). Although the pathogenesis of CIM has not been clearly defined, its relationship with the posterior fossa and CSC morphology is unclear. In this study, we aimed to perform morphometric analysis of both the posterior fossa and the CSC in CIM to investigate the correlation of measurements with each other and to reveal their effects on the development of syringomyelia (SM), which has not been previously reported.

**Methods:** Magnetic resonance imaging images of 90 patients and 30 healthy individuals were retrospectively analyzed. Posterior fossa parameters and CSC diameters at all cervical vertebral levels were measured for each patient. The taper ratio of CSC was calculated separately for each group at the C1-C4 and C1-C7 levels. The average CSC shape was drawn for each group.

**Results:** No statistically significant difference was detected between the age groups. A steeper taper ratio was detected when CIM was accompanied by SM. In addition, the posterior fossa had a narrower volume than the normal fossa in CIM.

**Conclusion:** Morphometric analysis of both the posterior fossa and the CSC was performed using CIM for the first time in the literature. This is the first study to present the term "tapering" with an illustration.

**Keywords:** Chiari malformation, posterior fossa, syringomyelia, morphometric analysis, taper ratio

## Introduction

Chiari malformation (CIM) is a congenital anomaly characterized by herniation of the hindbrain structures through the foramen magnum into the cervical spinal canal (CSC). Although there are different forms of CIM, the most common is type 1, which is characterized by displacement of the cerebellar tonsils toward the upper CSC and may be accompanied by syringomyelia (SM). Other types of CIM may also be accompanied by hydrocephalus, craniosynostosis, tethered spinal cord syndrome, and various bone abnormalities in addition to SM (1).

Although the pathogenesis of CIM has not been clearly defined, it has been hypothesized that the underdeveloped posterior fossa region creates congestion on the hindbrain, leading to herniation and SM formation, and various morphometric studies in the literature support this hypothesis (2-6). It has been reported that SM in CIM may occur as a result of abnormal cerebrospinal fluid (CSF) dynamics (7). In addition, previous studies have investigated the effect of the morphology of CSC on the development of SM in CIM (8-10). Although there are also studies in which morphometric analysis of the posterior fossa is performed in CIM (5,6,11), no study has evaluated morphometric analysis of both the posterior fossa and the CSC together. In this study, our aim was to perform morphometric analysis of both the posterior fossa and the CSC in CIM to investigate the correlation of measurements with each other and to reveal their effects on the development of SM.

## Methods

### Ethical Approval

This study was approved by the chairmanship of the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Haseki Training and Research Hospital (approval number: 65-2023, date: 29.03.2023).

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### Patients

Within the scope of this study, magnetic resonance imaging (MRI) of patients who applied to our hospital between 2014 and 2023 and were diagnosed with CIM and/or idiopathic SM were retrospectively examined. The cases were collected in 4 different groups. 30 patients with only CIM were included in Group 1, 30 patients with CIM and SM were included in Group 2, and 30 patients with idiopathic SM were included in Group 3. Thirty patients who applied to our hospital for a different reason were included in Group 4, which comprised the control group.

### Inclusion and Exclusion Criteria

The inclusion criterion for patients with CIM to be included in the study was determined as cerebellar tonsillar herniation >3 millimeters (mm) and above. The inclusion criterion for idiopathic SM was determined as the presence of cervical or cervicothoracic SM without pathology causing SM, such as cerebellar tonsillar herniation, neoplasm, trauma, and infection. Cases with a history of occipitocervical surgery, craniocervical trauma, spinal dysraphism, spinal cord disease other than SM, cervical degenerative disease narrowing the spinal subarachnoid space, significant cervical flattening and/or kyphosis, hydrocephalus, and peripheral nerve entrapment neuropathy were excluded from the study.

### Radiological Measurement

Radiological evaluation was performed using midsagittal T2 sequence MRI images of patients (GE Healthcare) scanned at 1.5 Tesla quality and 3 mm thickness. The degree of tonsillar herniation was calculated by considering the length (in mm) of the line drawn perpendicularly from the tip of the cerebellar tonsil to the line connecting the basion and opisthion.

For the morphometric analysis of the posterior fossa, clivus length (the line extending between the highest point of the dorsum sella and the basion), anteroposterior diameter of the foramen magnum (the line connecting the basion and the opisthion), supraocciput length (the line between the center of the internal occipital protuberance and the opisthion), posterior fossa diameter (line extending parallel to the basion-opisthion line from above the dorsum sella to the internal occipital protuberance), and posterior fossa height (line extending perpendicularly from the splenium to the basion-opisthion line) were measured separately for each patient and recorded in millimeters (Figure 1).

For the morphometric analysis of the CSC, the diameter of the spinal canal was measured at all cervical vertebral levels. To confirm the midsagittal view, we checked that the spinous processes were equally visible at all levels and that we were in the midline in the axial view. Measurements were performed by placing a line perpendicular to the spinal canal from the midpoint of the distance between the upper and lower endplates of the vertebra along the anteroposterior border of the subarachnoid space in the vertebrae, except for C2. Measurements at the C2 level were made by placing a line perpendicular to the spinal canal from the midpoint of the distance between the upper and lower endplates of the corpus along the anteroposterior border of the subarachnoid space (Figure 2). Using this method, the diameters of the spinal canal at levels C1-C7 were measured and were noted as mm in all groups. After measurement, a linear trend line was fitted by least squares regression with an algorithm resident in the Microsoft Excel spreadsheet (Microsoft, Redmond, Washington), and the slope of this line was recorded as the taper ratio (mm/level). The taper ratio was calculated separately for each group at the C1-C4 and C1-C7 levels.

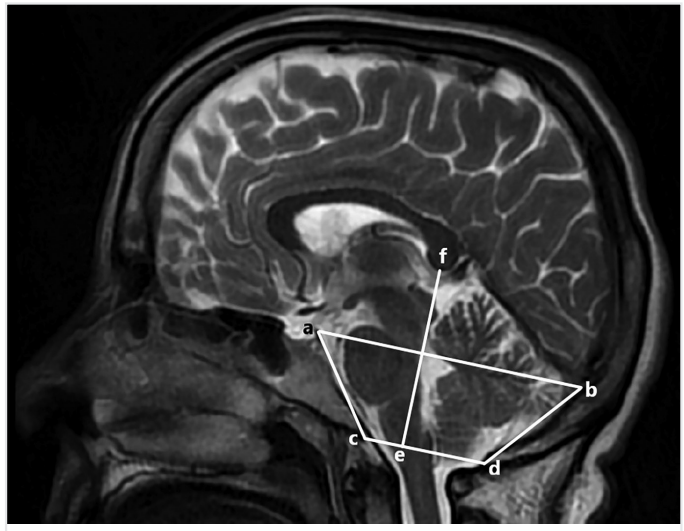


**Figure 1.** Posterior fossa measurement method made on mid-sagittal T2-weighted MRI of a healthy case
a: Dorsum sella, b: Center of the internal occipital protuberance, c: Basion, d: Opisthion, e: Contact point of the line perpendicular to the foramen magnum diameter, f: Inferior aspect of the splenium, a, b: Posterior fossa diameter, c, d: Foramen magnum diameter, a, c: Clivus length, b, d: Supraocciput length, e, f: Posterior fossa height
MRI: Magnetic resonance imaging

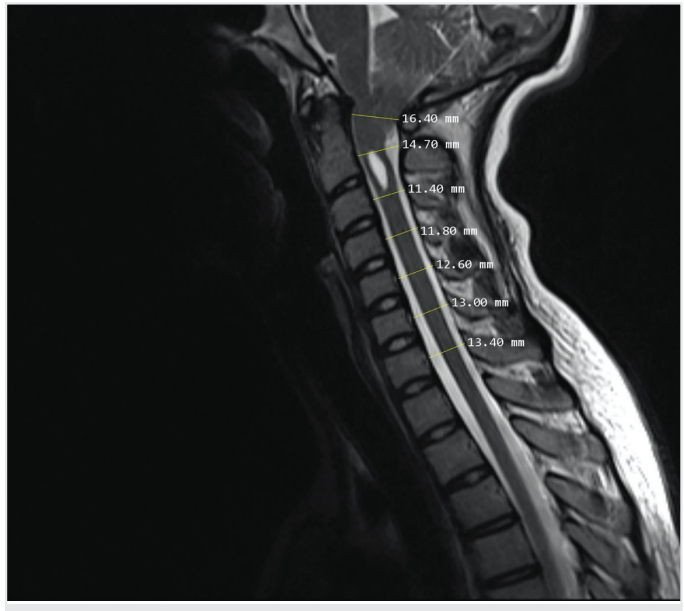


**Figure 2.** Cervical spinal canal measurement method using mid-sagittal T2-weighted MRI of a Group 2 case
MRI: Magnetic resonance imaging

### Illustration

The average CSC shape was drawn for each group using Adobe Illustrator 2022 (Adobe Inc., California, USA) based on the average foramen magnum diameters and average CSC diameters of the groups. Average vertebral height values reported in the literature were used for figure drawing. The average height values were accepted as 5 mm for C1 (12), the sum of 15.4 (posterior height of the odontoid) and 17.9 (posterior height of the body of C2) for C2 (13), and 10 mm for typical cervical vertebrae (14). When calculating the spinal canal diameter at the C1 level, the total thickness of the odontoid process and ligaments was maintained constant at 15 mm.

### Statistical Analysis

The Number Cruncher Statistical System (NCSS LLC, Kaysville, Utah, USA) 2020 statistical software for Windows was used to analyze the study data. We expressed quantitative variables as mean, standard deviation, median, minimum, and maximum values, and descriptive statistical methods, such as frequency and percentage, for qualitative variables. Shapiro-Wilks test and Box Plot graphics were used to evaluate the suitability of the data for normal distribution. Predictive values were obtained by linear regression analysis for the calculation of taper ratios. One-Way ANOVA was used to evaluate normally distributed variables according to groups, and Bonferroni's test was used for post hoc comparisons to determine the group that caused the difference. Pearson's chi-square test was used to compare qualitative data. The results were evaluated at the 95% confidence interval and the significance level was set as $p<0.05$.

## Results

The descriptive statistics of patients' age and gender by group are summarized in Table 1. No statistically significant differences were detected between the groups in terms of age distribution ($p>0.05$). The gender distribution was approximately 2:1 in favor of females (Table 1).

The anteroposterior diameter of the CSC was the narrowest at C4 across all groups. The level at which the groups were closest to each other in terms of CSC diameter was noted as the C3 level. The spinal canal narrowed from C1 to C4 in all groups. The taper ratios of Group 2 were noted to be significantly steeper than other groups ($p<0.01$). The taper ratios of Groups 1 and 3 were similar to those of Group 4 ($p>0.05$) (Table 2). It was noted that although the CSC diameter of 9 patients in Group 1 was similar to the diameter measurements in Group 2, SM did not develop. The trendline graphic obtained from the CSC diameter measurements of the Groups is shown in Figure 3. The taper ratios of the groups were also presented graphically (Figure 4). As a result of the illustration of the average foramen magnum diameter and average CSC diameters of the groups, it was noted that there was a rapid narrowing in Group 2 compared with the other groups, especially at the C1-C3 levels (Figure 5).

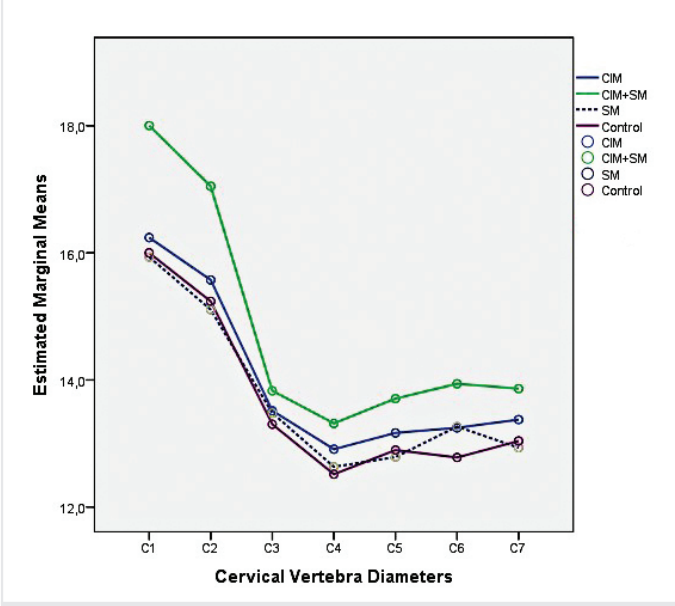


**Figure 3.** Trendline graph of cervical vertebral diameters according to groups
CIM: Chiari malformation, SM: Syringomyelia

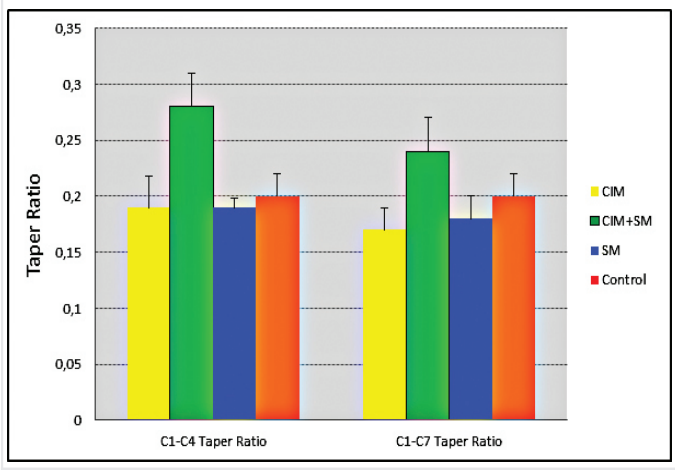


**Figure 4.** Distribution of C1-C4 and C1-C7 taper ratio values by groups
CIM: Chiari malformation, SM: Syringomyelia

**Table 1. Descriptive statistics of patients' age and sex by group**

| Groups | | Group 1 (CIM) (n=30) | Group 2 (CIM + SM) (n=30) | Group 3 (SM) (n=30) | Group 4 (control) (n=30) | p |
|---|---|---|---|---|---|---|
| Gender | Men | 9 (30.0) | 11 (36.7) | 13 (43.3) | 10 (33.3) | **0.737**[a] |
| | Women | 21 (70.0) | 19 (63.3) | 17 (56.7) | 20 (66.7) | - |
| Age | Mean ± SD | 38.03±6.62 | 38.3±7.41 | 41.77±8.31 | 37.4±8.04 | **0.172**[b] |
| | Median (min.-max.) | 37.5 (26-50) | 40 (24-51) | 41.5 (27-55) | 35.5 (19-49) | - |

[a]Pearson's chi-square test, [b]One-Way ANOVA test, CIM: Chiari malformation, SM: Syringomyelia, SD: Standard deviation, min.: Minimum, max.: Maximum

**Table 2. Descriptive statistics of cervical vertebra diameters and taper ratio**

| | | Group 1 [A]CIM (n=30) | Group 2 [B]CIM + SM (n=30) | Group 3 [C]SM (n=30) | Group 4 [D]control (n=30) | [b]p | A-B | A-C | A-D | B-C | B-D | C-D |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C1 | Mean ± SD | 16.24±0.79 | 18.00±0.88 | 15.93±0.75 | 16.00±0.59 | **0.001**** | **0.001** | 0.729 | 1,000 | 0.001 | **0.001** | 1,000 |
| | Median (min.-max.) | 16 (15.2-17.4) | 18.1 (16.4-19.7) | 15.8 (15-17.4) | 16 (15-17.5) | | | | | | | |
| C2 | Mean ± SD | 15.57±0.60 | 17.05±1.01 | 15.11±0.69 | 15.24±0.53 | **0.001**** | **0.001** | 0.088 | 0.460 | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 15.4 (14.8-16.7) | 17.2 (14.7-19) | 15 (14.1-16.4) | 15.1 (14.5-16.4) | | | | | | | |
| C3 | Mean ± SD | 13.52±0.62 | 13.83±0.80 | 13.48±0.63 | 13.30±0.44 | **0.016*** | 0.352 | 1,000 | 1,000 | 0.211 | **0.010** | 1,000 |
| | Median (min.-max.) | 13.5 (12.4-15.2) | 13.9 (11.4-15.1) | 13.2 (12.4-14.7) | 13.2 (12.8-14.2) | | | | | | | |
| C4 | Mean ± SD | 12.94±0.54 | 13.32±0.66 | 12.63±0.55 | 12.52±0.38 | **0.001**** | **0.027** | 0.307 | 0.036 | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 12.8 (12.2-14.4) | 13.5 (11.8-14.4) | 12.4 (12-13.6) | 12.5 (12-13.3) | | | | | | | |
| C5 | Mean ± SD | 13.17±0.63 | 13.71±0.61 | 12.79±0.67 | 12.90±0.38 | **0.001**** | **0.003** | 0.078 | 0.454 | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 13 (12.4-15) | 13.8 (12.6-14.6) | 12.5 (12-14.1) | 12.9 (12.3-13.7) | | | | | | | |
| C6 | Mean ± SD | 13.25±0.66 | 13.94±0.60 | 13.27±0.65 | 12.78±0.47 | **0.001**** | **0.001** | 1,000 | **0.019** | **0.001** | **0.001** | **0.013** |
| | Median (min.-max.) | 13 (12-14.9) | 13.9 (13-14.8) | 13.1 (12.5-14.6) | 12.8 (12.2-13.5) | | | | | | | |
| C7 | Mean ± SD | 13.38±0.68 | 13.86±0.63 | 12.93±0.62 | 13.04±0.40 | **0.001**** | **0.011** | **0.026** | 0.176 | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 13.2 (12.3-15) | 13.8 (12.8-15.1) | 12.8 (12.2-14.3) | 13 (12.3-13.8) | | | | | | | |
| C1-C4 taper ratio | Mean ± SD | 0.19±0.028 | 0.28±0.03 | 0.19±0.02 | 0.20±0.02 | [b]**0.001**** | **0.001** | 1,000 | 0.593 | **0.001** | **0.001** | 0.630 |
| | Median (min.-max.) | 0.20 (0.12-0.25) | 0.27 (0.20-0.34) | 0.19 (0.16-0.22) | 0.20 (0.17-0.25) | | | | | | | |
| C1-C7 taper ratio | Mean ± SD | 0.17±0.02 | 0.24±0.03 | 0.18±0.02 | 0.17±0.02 | [b]**0.001**** | **0.001** | 1,000 | 1,000 | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 0.17 (0.14-0.21) | 0.24 (0.18-0.32) | 0.17 (0.13-0.22) | 0.18 (0.14-0.23) | | | | | | | |

[b]One-way ANOVA & post-hoc Bonferroni test, *p<0.05, **p<0.01. CIM: Chiari malformation, SM: Syringomyelia, SD: Standard deviation

When the posterior fossa measurement results of the groups were compared, it was calculated that the height, posterior fossa diameter, supraocciput, and clivus length were statistically smaller in Groups 1 and 2 than in Groups 3 and 4 (p<0.01). In contrast, the foramen magnum diameter length was statistically larger in Groups 1 and 2 than in Groups 3 and 4 (p<0.01). Comparing all Groups, Group 2 had the narrowest posterior fossa, and Group 1 had the narrowest posterior fossa (Table 3).

## Discussion

Despite its long history, the pathophysiology of CIM is still not clearly understood, and its treatment remains controversial (15). The opinions are contradictory, especially regarding patients who are asymptomatic or have a mild clinical course. The presence of SM in these patients affects the surgical decision (16). However, there are also case reports in the literature stating that SM and tonsillar herniation can be spontaneously resolved in CIM (17-21). There are many hypotheses regarding the pathophysiology of SM, but the most accepted one is that CSF enters the central canal with arterial pulsation but cannot return because the narrowed part of the central canal acts as a one-way valve (22).

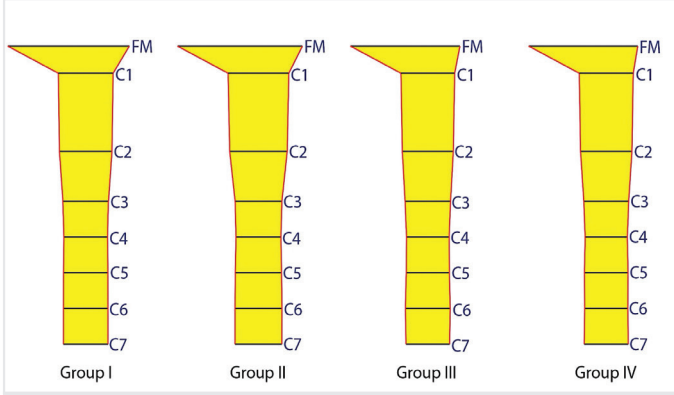


**Figure 5.** Illustration showing the average foramen magnum diameter and average cervical spinal canal diameters of the groups

Conversely, no relationship could be established between the degree of herniation in CIM and the severity of complaints (6,23).

Research is ongoing to resolve the debates regarding both etiopathogenesis and treatment strategies in CIM. Some of these analyses are morphometric analyses performed on radiological data.

**Table 3. Descriptive statistics of the posterior fossa measurements**

| | | Group 1 [A]CIM (n=30) | Group 2 [B]CIM + SM (n=30) | Group 3 [C]SM (n=30) | Group 4 [D]control (n=30) | Toplam | [b]p | A-B | A-C | A-D | B-C | B-D | C-D |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Height | Mean ± SD | 54.62±3.81 | 53.36±3.05 | 62.44±5.54 | 61.92±3.79 | 58.09±5.82 | **0.001**** | 1,000 | **0.001** | **0.001** | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 53.5 (49.5-61.7) | 53.2 (48.9-58.9) | 60 (54.3-71.1) | 61.3 (55.5-68) | 57.7 (48.9-71.1) | | | | | | | |
| Foramen magnum | Mean ± SD | 36.05±2.49 | 37.04±2.20 | 32.49±2.18 | 32.35±1.54 | 34.48±2.97 | **0.001**** | 0.460 | **0.001** | **0.001** | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 36.3 (31.6-40.1) | 37 (33.5-40.8) | 32.4 (29.1-36.3) | 32.3 (29.8-36.4) | 34.1 (29.1-40.8) | | | | | | | |
| Posterior fossa diameter | Mean ± SD | 75.49±4.24 | 74.18±4.42 | 85.41±6.34 | 86.96±1.80 | 80.51±7.26 | **0.001**** | 1,000 | **0.001** | **0.001** | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 76.8 (68.3-81) | 74.8 (65.1-82.8) | 85.3 (71.6-94.1) | 86.6 (84.3-90.2) | 80.6 (65.1-94.1) | | | | | | | |
| Supraocciput | Mean ± SD | 42.11±4.88 | 41.09±2.76 | 50.85±2.79 | 49.68±2.41 | 45.93±5.49 | **0.001**** | 1,000 | **0.001** | **0.001** | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 41.8 (34.7-49.9) | 41.2 (37.1-46.4) | 50.4 (47.1-56.1) | 49.1 (45.5-54) | 47.1 (34.7-56.1) | | | | | | | |
| Clivus | Mean ± SD | 39.61±5.08 | 36.34±6.32 | 44.94±2.77 | 46.25±2.85 | 41.78±6 | **0.001**** | **0.036** | **0.001** | **0.001** | **0.001** | **0.001** | 1,000 |
| | Median (min.-max.) | 39.6 (32.6-46.8) | 33.7 (28.1-44.7) | 44.4 (40.1-49.4) | 45.5 (41.5-51.3) | 43.4 (28.1-51.3) | | | | | | | |

[b]One-Way ANOVA and Bonferroni tests, **p<0.01, CIM: Chiari malformation, SM: Syringomyelia, SD: Standard deviation

While some authors focused on the morphometric analysis of the posterior fossa, others focused on the morphometric analysis of the CSC. As a result of the measurements, the authors generally stated that there was a decrease in the measurement values of the posterior fossa compared with normal and that this situation leads to congestion in the posterior fossa, causing herniation (5,6,24-26). Basaran et al. (27) drew attention to another point in their morphometric analysis of CIM. They reported that the posterior fossa volume was normal in CIM, but because the total intracranial volume increased compared with normal, the pathophysiology was processed due to a proportional decrease in the posterior fossa volume.

Studies on the morphometric analysis of the CSC in CIM are generally concerned with the extent to which the diameter of the spinal canal narrows. The results of the studies conducted on this subject do not agree with each other. Thompson et al. (28) compared the C1-4, C4-7, and C1-7 taper ratios of CIM + SM with those of CIM and found that the CIM + SM group had a steeper taper ratio in the C4-7. According to this result, the authors hypothesized that the morphology of the lower cervical region may lead to the development of SM. Hirano et al. (8) compared the C1-7 taper ratio between CIM + SM, CIM, SM, and healthy individuals. In the analysis, it was determined that there was a steeper taper ratio in the upper CSC in CIM + SM than in other regions, and it was noted that there was a mesodermal anomaly in CIM (8). Gadde et al. (10) investigated the role of the taper ratio in the transformation of presyrinx to SM in CIM and found that the taper ratios at C1-4 and C1-7 were steeper in patients with presyrinx. Zhu et al. (9) drew attention to a different point and compared the taper ratio in distended SM with that in non-distended SM and stated that, contrary to other studies, the taper ratio was steeper in the non-distended group. Hammersley et al. (29) drew attention to yet another point and compared CIM patients with and without scoliosis; in their analysis, they stated that there was a steeper taper ratio in those with scoliosis and CIM. Thakar et al. (30) analyzed both the taper ratio and the changes in the paraspinal muscles in CIM. They stated, similar to the literature, that there is a steeper tapering in CIM; there is also atrophy in the paraspinal muscles, and this atrophy may be related to the steeper tapering (30).

The results of all these studies suggest that the morphology of CIM is different from normal. Although there have been many morphometric analyses in CIM of the posterior fossa and the CSC, no study has been conducted regarding both the posterior fossa and the CSC morphometry in the literature. In this study, unlike previous studies, measurements were made for both regions, and the results were evaluated together. According to our findings, posterior fossa dimensions are generally reduced in CIM with or without SM. It is also understood that when SM is accompanied by CIM, the posterior fossa dimensions become narrower. Our findings regarding spinal canal morphometry indicate a relationship between SM accompanying CIM and steeper tapering. Although there are many studies on spinal canal tapering in CIM, this study presents the term "tapering" with an illustration for the first time in the literature. The aim of this study was to better understand the effect of tapering on the development of SM. However, it was observed that the CSC diameters of 9 patients in Group 1 were similar to those of the patients in Group 2. Nevertheless, SM did not develop in these

patients. Based on these findings, CSC morphology alone may not be sufficient for the development of SM. In this regard, a prospective study with long-term follow-up of patients with tapering rates similar to those in Group 2 may help early detect patients with CIM who are likely to develop SM in the future. We believe that studies with a larger patient population are necessary.

### Study Limitations

This retrospective study was based on radiological data. Further prospective studies with a larger patient group, including clinical information and long-term follow-up.

## Conclusion

In this study, for the first time in the literature, morphometric analysis of both the posterior fossa and the CSC was performed using CIM. Consistent with the literature, our results showed that both the posterior fossa and CSC morphometry were different between CIM and normal subjects. In addition, although there are many studies on the CSC taper ratio, this is the first study to present the term "tapering" with an illustration. We believe that our results will help reduce the debate about the etiology and treatment of CIM.

**Ethics Committee Approval:** This study was approved by the chairmanship of the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Haseki Training and Research Hospital (approval number: 65-2023, date: 29.03.2023).

**Informed Consent:** Retrospective study.

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

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

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## References

1. George TM, Higginbotham NH. Defining the signs and symptoms of Chiari malformation type I with and without syringomyelia. Neurol Res. 2011; 33: 240-6.
2. Milhorat TH, Nishikawa M, Kula RW, Dlugacz YD. Mechanisms of cerebellar tonsil herniation in patients with Chiari malformations as guide to clinical management. Acta Neurochir (Wien). 2010; 152: 1117-27.
3. Sgouros S, Kountouri M, Natarajan K. Posterior fossa volume in children with Chiari malformation Type I. J Neurosurg. 2006; 105: 101-6.
4. Tubbs RS, Hill M, Loukas M, Shoja MM, Oakes WJ. Volumetric analysis of the posterior cranial fossa in a family with four generations of the Chiari malformation Type I. J Neurosurg Pediatr. 2008; 1: 21-4.
5. Nishikawa M, Sakamoto H, Hakuba A, Nakanishi N, Inoue Y. Pathogenesis of Chiari malformation: a morphometric study of the posterior cranial fossa. J Neurosurg. 1997; 86: 40-7.
6. Aydin S, Hanimoglu H, Tanriverdi T, Yentur E, Kaynar MY. Chiari type I malformations in adults: a morphometric analysis of the posterior cranial fossa. Surg Neurol. 2005; 64: 237-41.
7. Pinna G, Alessandrini F, Alfieri A, Rossi M, Bricolo A. Cerebrospinal fluid flow dynamics study in Chiari I malformation: implications for syrinx formation. Neurosurg Focus. 2000; 8: E3.
8. Hirano M, Haughton V, Munoz del Rio A. Tapering of the cervical spinal canal in patients with Chiari I malformations. AJNR Am J Neuroradiol. 2012; 33:1326-30.
9. Zhu Z, Sha S, Sun X, Liu Z, Yan H, Zhu W, et al. Tapering of the cervical spinal canal in patients with distended or nondistended syringes secondary to Chiari type I malformation. AJNR Am J Neuroradiol. 2014; 35: 2021-6.
10. Gadde JA, Shah V, Liebo GB, Ringstad GA, Pomeraniec IJ, Bakke SJ, et al. Anatomical features of the cervical spinal canal in Chiari I deformity with presyrinx: A case-control study. Neuroradiol J. 2017; 30: 405-9.
11. Noudel R, Jovenin N, Eap C, Scherpereel B, Pierot L, Rousseaux P. Incidence of basioccipital hypoplasia in Chiari malformation type I: comparative morphometric study of the posterior cranial fossa. Clinical article. J Neurosurg. 2009; 111: 1046-52.
12. Gosavi SN, Vatsalaswamy P. Morphometric Study of the Atlas Vertebra using Manual Method. Malays Orthop J. 2012; 6: 18-20.
13. Naderi S, Arman C, Güvençer M, Korman E, Senoglu M, Tetik S, et al. Morphometric analysis of the C2 body and the odontoid process. Turkish Neurosurgery. 2006; 16: 14-8.
14. Prameela MD, Prabhu LV, Murlimanju BV, Pai MM, Rai R, Kumar CG. Anatomical dimensions of the typical cervical vertebrae and their clinical implications. Eur J Anat. 2020; 24: 9-15.
15. Frič R, Eide PK. Chiari type 1-a malformation or a syndrome? A critical review. Acta Neurochir (Wien). 2020; 162: 1513-25.
16. Massimi L, Peretta P, Erbetta A, Solari A, Farinotti M, Ciaramitaro P, et al. Diagnosis and treatment of Chiari malformation type 1 in children: the International Consensus Document. Neurol Sci. 2022; 43: 1311-26.
17. Cuthbert H, Pepper J, Price R. Spontaneous resolution of a Chiari malformation with syringomyelia. BMJ Case Rep. 2021; 14: e241789.
18. Gallo E, Rahmathulla G, Rao D, Tavanaiepour K, Tavanaiepour D. Spontaneous syrinx resolution in patient with Chiari I malformation: illustrative case. J Neurosurg Case Lessons. 2021; 1: CASE21236.
19. Sun PP, Harrop J, Sutton LN, Younkin D. Complete spontaneous resolution of childhood Chiari I malformation and associated syringomyelia. Pediatrics. 2001; 107: 182-4.
20. Avellino AM, Britz GW, McDowell JR, Shaw DW, Ellenbogen RG, Roberts TS. Spontaneous resolution of a cervicothoracic syrinx in a child. Case report and review of the literature. Pediatr Neurosurg. 1999; 30: 43-6.
21. Strahle J, Muraszko KM, Kapurch J, Bapuraj JR, Garton HJ, Maher CO. Natural history of Chiari malformation Type I following decision for conservative treatment. J Neurosurg Pediatr. 2011; 8: 214-21.
22. Koyanagi I, Houkin K. Pathogenesis of syringomyelia associated with Chiari type 1 malformation: review of evidences and proposal of a new hypothesis. Neurosurg Rev. 2010; 33: 271-84.
23. Aboulezz AO, Sartor K, Geyer CA, Gado MH. Position of cerebellar tonsils in the normal population and in patients with Chiari malformation: a quantitative approach with MR imaging. J Comput Assist Tomogr. 1985; 9: 1033-6.
24. Vurallı D, Oksüzler M. Radiological determination of fossa cranii posterior morphometry in Chiari malformation type I. Cukurova Medical Journal. 2022; 47: 1067-72.
25. Dagtekin A, Avci E, Kara E, Uzmansel D, Dagtekin O, Koseoglu A, et al. Posterior cranial fossa morphometry in symptomatic adult Chiari I malformation patients: comparative clinical and anatomical study. Clin Neurol Neurosurg. 2011; 113: 399-403.

26. Yan H, Han X, Jin M, Liu Z, Xie D, Sha S, et al. Morphometric features of posterior cranial fossa are different between Chiari I malformation with and without syringomyelia. Eur Spine J. 2016; 25: 2202-9.

27. Basaran R, Efendioglu M, Senol M, Ozdogan S, Isik N. Morphometric analysis of posterior fossa and craniovertebral junction in subtypes of Chiari malformation. Clin Neurol Neurosurg. 2018; 169: 1-11.

28. Thompson A, Madan N, Hesselink JR, Weinstein G, Munoz del Rio A, Haughton V. The Cervical Spinal Canal Tapers Differently in Patients with Chiari I with and without Syringomyelia. AJNR Am J Neuroradiol. 2016; 37: 755-8.

29. Hammersley J, Haughton V, Wang Y, del Rio AM. Tapering of the cervical spinal canal in patients with scoliosis with and without the Chiari I malformation. AJNR Am J Neuroradiol. 2012; 33: 1752-5.

30. Thakar S, Kurudi Siddappa A, Aryan S, Mohan D, Sai Kiran NA, Hegde AS. Does the mesodermal derangement in Chiari Type I malformation extend to the cervical spine? Evidence from an analytical morphometric study on cervical paraspinal muscles. J Neurosurg Spine. 2017; 27: 421-7.

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# Effect of Cerebral Dominance on Postoperative Pain

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## ABSTRACT

**Introduction:** In this study, we aimed to determine the functional dominance of the right and left hemispheres of the operated patients and the effectiveness of postoperative pain therapy when the patients underwent surgery on the same or different sides with the dominant hemisphere.

**Methods:** The patients were given a Miles test for the dominant eye in the preoperative period and were instructed while the key was in front of the patient to take the key and open the door to determine the dominant hand. For the dominant foot, the patient was given the command of "move your foot" in a calm environment and accepted as the foot that he carried the dominant foot. After routine spinal anesthesia and elective knee arthroplasty surgery, patients underwent Patient Controlled Analgesia device, 24$^{th}$ hour Numeric Rating Scale (NRS) scores, and the amount of total applied analgesic and additional analgesic were recorded.

**Results:** When the clinical characteristics of the patients were examined, there were 38 patients on the right side of the dominant eye, 34 on the left side, 67 on the right hand dominant side, 5 on the left side, 49 on the right foot dominant side, and 23 on the left side. The NRS score on the surgical side was compared with the dominant foot, dominant eye, and dominant hand. There was no statistically significant difference between the NRS pain scale and other variables except those opposed to the dominant eye ($p>0.05$). The NRS pain scale median (median: 3.0) was found to be significantly lower in patients who were operated on the same side as the dominant eye ($p=0.016$).

**Conclusion:** According to the results of our study, the NRS score was not changed in patients operated on the same side of the dominant foot and hand, whereas the NRS score was lower in patients operated on the same side with the dominant eye.

**Keywords:** Dominant hemisphere, postoperatif pain, cerebral lateralization

## Introduction

Cerebral lateralization is described as anatomical and functional differentiation between the right and left hemispheres of the brain. The left hemisphere undertakes functions associated with verbal expression, such as reading, speaking, and using verbal symbols. The right hemisphere is associated with the acceptance and storage of visual data, visual and tactile recognition of shapes and forms, and orientation and perspective of the shapes (1).

One hemisphere is more dominant than the other is an anatomic lateralization and the hand-foot preference are considered functional lateralization. When we look at the laterality of pain neuroimaging studies of human pain have revealed a common "pain matrix" spreading into both hemispheres of the brain (2-5); however, specific findings suggest that the right hemisphere plays an important role in pain perception (6).

In this study, we performed hand, eye, and foot dominance tests on patients who underwent surgery and investigated whether there was an increase in postoperative pain on the dominant side according to the dominance of the right and left half of the body.

## Methods

After approval of the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 1061, date: 04.08.2017, and informed consent of the patients, between August 2017 and February 2018, 80 patients were included in our prospective study evaluating the effect of dominant cerebral hemisphere on postoperative pain in knee arthroplasties. The sample was calculated using G*power 3.0 software, and the mean pain between the dominant and non-dominant side operations was 1.0±0.3 (3.5±1.5 and 4.5±1.8 respectively). The difference was estimated, and a total of 70 people were found to be sufficient with a 5% alpha error (type 1 error) and 80% power. Patients undergoing elective surgery with spinal anesthesia in the American Society of Anesthesiologists (ASA) classification 1-3 group were included in the study. Patients with dementia, diabetes mellitus, a history of cerebrovascular disease, degenerative nerve diseases, who cannot adapt to Patient Controlled Analgesia (PCA) machine, who do not want regional anesthesia or are under contraindication to regional anesthesia, who are given general anesthesia or have returned to general anesthesia, ASA4 and emergency patients, patients who could not use

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PCA due to excessive nausea, or patients with device failure were excluded from the study.

Before surgery, the dominant hand, dominant eye, and dominant foot determination tests were performed. For that purpose of evaluating the dominant eye, the patients were asked to hold both arms forward, unite their hands at eye level, and look at an object 6 meters away from the triangle formed by bringing both the head and index fingers to the tip (modified Miles test) (7-9). To determine the dominant hand, instead of a questionnaire, inspired by Oldfield's Edinburgh Scale, the patient was asked to take the key from a box remaining in front of him and open the door with that key (10). In this test, the hand used to open the door was accepted as the dominant hand. The dominant foot was asked by male patients if they had played football. If the answer was "yes", then the participant was asked for foot preference. Other patients in the sitting position in a calm environment with eyes closed "Move toes" command was given to the foot and moving foot. Determined as dominant. Patients who played both feet at the same time, or asked "which" question to play, were asked to hit a ball placed on both feet with one foot while sitting. For the performance test, Coren and Porac (11) was inspired by the various works he has conducted since 1978. All patients were informed about Numeric Rating Scale (NRS), PCA and how to use the PCA device.

The NRS is a pain scaling system commonly used to evaluate pain severity. It is asked to the patient to describe her/his pain by giving a number between 010, with zero meaning "no pain" and 10 meaning "the worst pain imaginable" (12).

Routine, standard anesthesia monitoring (3-lead ECG, non-invasive arterial blood pressure, pulse oximetry) was provided to the patients, and after the vascular access was opened, a sitting position was provided, providing aseptic conditions, a 25-gauge spinal needle (Quincke 25-gauge Spinal, Egemen International) from the L3-4 intervertebral space was pushed forward to the subarachnoid space. By observing the free development of cerebrospinal fluid when the needle reached the subarachnoid space, spinal anesthesia was performed using 12.5 mg of bupivacaine (buvasin 0.5% spinal heavy VEM drug). Patients were then laid on the side for surgery, and the operation was started after the sensory and motor block levels were checked. At the end of the operation, patients were taken to the recovery room and intravenous PCA device was inserted and sent to the service. Tramadol was used at a concentration of 4 mg/mL during preparation of the intravenous PCA device. The device was programed with a bolus dose of 10 mg and continuous infusion of 10 mg/h for 20 min with a locking time of 20 min. Paracetamol (1 g) (parol intravenous 10 mg/mL 100 mL vial Atabay drug) and/or dexketoprofen (dexalgine 50 mg/2 mL Nobel drug) were administered as additional analgesics to patients with resting pain. During the first 24 hours after the operation NRS scores, total analgesic use, and additional analgesic need were recorded according to postoperative follow-up forms.

### Statistical Analysis

The statistical analysis was performed using SPSS version 15.0 software. Parametric data were analyzed using Student's t-test, and non-parametric data were analyzed with Mann-Whitney U test. While descriptive analyses were presented, mean, standard deviation, median and minimum-maximum values were used. $P<0.05$ was considered statistically significant.

## Results

Of the 80 patients who participated in the study, 6 had to have general anesthesia for various reasons and 2 patients were excluded because of PCA machine faults.

Of the 72 patients included in the study, 60 (83.3%) were female and 12 were male. The mean age was 63.1±4.3. The mean body mass index (BMI) was 31.9±2.5 years (Table 1).

Clinical characteristics of the patients participating in the study examined 40 people from the left knee, 32 people from the right knee, 38 people with right eye on the right side, 34 people on the left side, 67 people on the right hand side, 67 people on the right hand side, 5 people on the left side, 5 people on the left side 49 people with left side are 23 people (Table 1).

NRS 3-4, the targeted pain level, was reached in all patients. There was no statistically significant difference between the NRS pain scale scores and the other variables except those operated on the same side with the dominant eye ($p>0.05$). The median NRS pain scale score (median: 3.0) was significantly lower in patients who underwent surgery on the same side of the dominant eye than in the non-operative group (median: 4.0) ($p=0.016$) (Table 2).

**Table 1. Demographic data and clinical characteristics of patients**

| | | n/Mean ± SD* | %/(max.-min.)* |
|---|---|---|---|
| Gender | Female | 60 | 83.3 |
| | Male | 12 | 16.7 |
| Age* | | 63.1±4.3* | 63 (54.0-73.0)* |
| BMI* | | 31.9±2.5* | 32 (27.0-38.0)* |
| Operation side | Right/left | 32/40 | 44.4/55.5 |
| Eye dominance | Right/left | 38/34 | 52.77/47.22 |
| Hand dominance | Right/left | 67/5 | 90.03/7.46 |
| Foot dominance | Right/left | 49/23 | 68.05/31.94 |

*In the measurement data, instead of n, mean ± standard deviation, instead of (%) median, minimum, and maximum values are given, BMI: Body mass index, SD: Standard deviation, max.: Maximum, min.: Minimum

**Table 2. Comparison of NRS pain scale score and tramadol consumption in patients who operated on the same side with the dominant foot, dominant eye, and dominant hand**

| | NRS | | | p* | Consumption of tramadol (mg) | | p* |
|---|---|---|---|---|---|---|---|
| | Mean ± SD | | Median (min.-max.) | | Mean ± SD | Median (min.-max.) | |
| Operation on the same side as the dominant foot | Yes | 3.8±1.3 | 3.0 (3.0-8.0) | 0.901 | 328±64.2 | 200-400 | 0.536 |
| | No | 4.0±1.6 | 3.0 (3.0-10.0) | | 318±66.1 | 131-400 | |
| Operation on the same side as the dominant eye | Yes | 3.6±1.5 | 3.0 (3.0-10) | **0.016** | 314±65.2 | 131-400 | 0.353 |
| | No | 4.2±1.6 | 3.0 (3.0-8.0) | | 328±65.4 | 198-400 | |
| Operation on the same side as the dominant hand | Yes | 4.1±1.6 | 3.0 (3.0-8.0) | 0.301 | 330±60.3 | 200-400 | 0.355 |
| | No | 3.8±1.5 | 3.0 (3.0-10) | | 315±68.8 | 131-400 | |

*Mann-Whitney U test, min.: Minimum, max.: Maksimum, SD: Standard deviation, NRS: Numeric Rating Scale

The amount of tramadol used by the patient-controlled analgesia device in 24 hours was compared with the amount used in the dominant foot, dominant eye, and dominant hand. Accordingly, there was no statistically significant difference in the total amount of tramadol (mg) used between the groups ($p>0.05$) (Table 2).

## Discussion

The aim of our study was to evaluate the relationship between postoperative pain and eyes, hand, and foot dominance in patients who underwent arthroplasty under spinal anesthesia for knee osteoarthritis (OA).

Knee OA is the most common form of arthritis, and its prevalence is increasing., approximately 40% of the adult population over the age of 65 years has knee OA. Obesity and increased BMI are risk factors for OA (12,13).

The characteristics of the patients included in our study.

The mean age was 63. One year, and 83.3% of the patients were women. Our results regarding age and sex characteristics are consistent with the literature. The BMI was found to be 31.9±2.5 kg/m$^2$, and most patients were obese.

Pain is the most common symptom of knee OA. Macrotrauma or recurrence microtrauma may damage the articular cartilage. Chondrocytes react to this damage by releasing disintegrating enzymes and inducing a repair response. Thus, mechanical and nociceptive chronic pain occurs (14-16).

Neuropathic pain is also noted in individuals with long-lived symptoms duration. Surgical treatment is indicated for patients with advanced OA who do not respond to conservative treatment, and knee arthroplasty is performed (17).

Although knee arthroplasty is an effective and reliable surgical treatment, severe acute pain is observed in patients after surgery, and the incidence of chronicity is high if the acute pain is treated inadequately. In a previous study, showed that 35% of patients who underwent knee arthroplasty experienced continued pain complaint for 1 year postoperatively (18). Therefore, acute postoperative pain treatment after knee arthroplasties is provided by multimodal analgesia, including regional anesthesia techniques. Neuroaxial anesthesia (epidural, spinal anesthesia), which is an important component of multimodal analgesia, has a effects on mortality and morbidity in the perioperative period (19). With good pain control with multimodal analgesia, postoperative opioid consumption is reduced and rehabilitation. In our study, the NRS score was 3-4 in patients included in the study.

As distinct from the literature in our study, the relationship between cerebral laterality and pain after arthroplasty was evaluated.

One hemisphere is more dominant than the other is an anatomic lateralization and the hand-foot preference are considered functional lateralization.

Similar to hand preference, ie, the dominance of the foot, eye, and even the ear dominance is defined. In general, right eye dominance is observed in those who use the right hand was dominated more. Similarly, the right foot is dominant over the right handness (20,21).

In the examinations, it was understood that the preferences of the parents or educators changed the preferences of the hand and foot, which were contrary to the biological structure. However, eye preference does not change with education, social pressure, or other environmental factors. The choice of the eye preserves its natural nature (22).

When the clinical features of the patients who participated in the study were examined, 38 patients with right-sided eye dominance, 34 with left-sided eye dominance, 67 with right hand dominance, 5 with left-sided hand dominance, 49 with right foot dominance, and 23 with left foot dominance were found.

The left side is used negatively in many cultures and is interpreted as unfortunate. This makes it difficult to identify left foot and left hand dominance in social development. In particular, in our patients, motor activity at an advanced age was strengthened, and the functional difference between the two extremities decreased. The brain compensates for the decrease in the function of the limb, which it is conditioned not to use. Therefore, we thought that it would be difficult to evaluate the results of the questionnaire tests based on the patient queries, which are used in the literature, in all of our patients who were of advanced age. In addition, because our patients have orthopedic problems and have already experienced chronic pain and movement limitations for many years in both lower limbs, we have not been able to perform lower extremity tests on healthy volunteers. However, we were pleased to find that the results of our hand, eye, and foot dominance test were consistent with the dominance results in the abovementioned studies.

Functional magnetic resonance imaging studies by Symonds et al. (23) 5 of 9 brain regions associated with pain were activated in the right hemisphere during acute pain, demonstrating the dominance of the right hemisphere in the perception of pain.

Some studies have tried to explain the role of hemispheric activation in depression and pain (24). They hypothesized that the right hemisphere is specialized in activating and processing negative affective stimuli, and this specialization may play a role in the emergence of depression and pain. In order to evaluate the relationship between depression, experimental pain, and cerebral laterality, the researchers included 16 depressed and 16 normal girls who used their right hands in their studies. The suggestion that the right hemisphere mediates the coexistence of pain and depression is not supported; however, specific findings suggest that the right hemisphere plays an important role in pain perception.

Recent biochemical and behavioral data suggest that the right hemispheric lateralization of the amygdala during pain. Pain-related neuroplasticity in the laterocapsular division of the central nucleus of the amygdala in the right brain hemisphere has also been demonstrated. Ji and Neugebauer (25) evaluated electrophysiological pain perception before and after the induction of arthritis pain in rats using experimental models.

Short-term harmless and harmful test stimuli were applied to the peripheral, ipsilateral, and contralateral recording regions. A monoarthritis was created by intraarticular injection of kaolin and Irish moss into the rope or contralateral knee. Under normal conditions, neurons in the left amygdala were shown to have smaller recipient sites than those in the right amygdala; however, there was no difference in terms of pain perception. In another study, it was shown that right frontal brain hyperactivity can be used as a biological marker for increased pain sensitivity and has a negative effect (26). Merskey and Watson (27) showed that patients felt more pain on the left side of the body. They also pointed out that psychological pain was seen especially on the left side.

According to the results of our study, the NRS score was not changed in patients operated on the same side of the dominant foot and hand, whereas the NRS score was lower in patients operated on the same side with the dominant eye.

In a study of Lugo 328 right- and 22 left-handed patients, thermal noxious stimulus showed that while the majority of the cases used the right hand, the Visual Analogue Scale (VAS) score was significantly higher in the left hand (right hemisphere dominance). Previous studies reported high VAS scores on the left side (27-33). But the interesting thing is that 65% of the left side, irrespective of the dominance of the right or left hand, feels more painful on the left side. Researchers have suggested that the right hemisphere is predominantly involved in pain perception (34).

Our study was a clinical study that aimed to evaluate acute pain and chronic pain. Our study group consists of elderly patients with chronic pain instead of healthy volunteers; thus, our results may be different. The absence of functional imaging is an important limitation. Another limitation is that social pressures and beliefs affect hand and foot preferences. Extremity dominance may have disappeared in older people, such as our patients.

In this study, no significant correlation was found between the severity of perceived postoperative pain and the extremity dominance. Lower pain scores were observed only on the dominant eye side. In addition, there was no statistically significant difference between the tramadol use and operation sides. Although NRS is an effective method for pain assessment, it may have been insufficient in this study. It would be more accurate to assess the characteristics of the pain (type of pain, duration of intolerance, pain-related pain, behavior, anxiety score, etc.). In addition, OA is associated with chronic pain for a long time. When the pain becomes chronic, it can be accompanied by different problems, such as depression, anxiety, sleep disorders, attention, and memory changes (right hematologic dominance), which affect the threshold, perception, and severity of pain. In a review by Lithwick et al. (35), more common contralateral activation was observed in patients with chronic pain compared with acute pain in which the ipsilateral side was activated. Several studies have shown that chronic pain of psychological origin is especially on the left side (right hemisphere dominance) (33,36).

### Study Limitations

This was a clinical study, and it was intended to evaluate acute pain in patients with chronic pain. Our study group consists of elderly patients with chronic pain instead of healthy volunteers; thus, our results may be different. The absence of functional imaging is an important limitation. Another limitation is that social pressures and beliefs affect hand and foot preferences. Extremity dominance may have disappeared in older people, such as our patients.

## Conclusion

The postoperative pain scores of patients who underwent surgery on the same side with the dominant eye were low. We believe that our findings should be validated in studies in which similar clinical parameters and high validation scales are considered and functional imaging or electrophysiological evaluations are performed.

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 1061, date: 04.08.2017).

**Informed Consent:** It was obtained.

**Authorship Contributions:** Surgical and Medical Practices - M.K., Y.Ç.A.; Concept - Y.Ç.A.; Design - Y.Ç.A., V.E.; Data Collection or Processing - M.K.; Analysis or Interpretation - Y.Ç.A., V.E.; Literature Search - Y.Ç.A.; Writing - M.K., Y.Ç.A.

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## References


1. Nicholas P, La Mendola A. Peripheral and cerebral asymmetries in the rat. Science. 1997; 278: 31-4.
2. Casey KL. Forebrain mechanism of nociception and pain: analysis through imaging. Proc Natl Acad Sci USA. 1990; 96: 7668-74.
3. Davis KD. Pain imaging. Progress in Pain Research and Management, Volume 18. In: Casey KL, Bushnell MC (eds). International Association for the Study of Pain, Seattle, Washington, USA, 2000; p. 239.
4. Ingvar M. Pain and functional imaging. Philos Trans R Soc Lond B Biol Sci. 1999; 354: 1374-58.
5. Peyron R, Garcie-Larrea L, Gregoire M, Convers P, Richard A, Lavenne F, et al. Parietal and cingulate processes in central pain. A combined positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) study of an unusual case. Pain. 2000; 84: 77-87.
6. Symonds LL, Gordon NS, Bixby JC, Mande MM. Right-lateralized pain processing in the human cortex: an FMRI study. J Neurophysiol. 2006; 95: 3823-30.
7. Miles WR. Ocular dominance demonstrated by unconscious sighting. Journal of Experimental Psychology. 1929; 12: 113-26.
8. Miles WR Ocular dominance in human adults. Journal of General Psychology. 1930; 3: 412-29.
9. Valle-Inclan F, Blanco MJ, Soto D, Leiros L. A new method to assess eye dominance. Psicologica. 2008; 29: 55-64.
10. Oldfield RC. The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia. 1971; 9: 97-113.
11. Coren S, Porac C. The validity and reliability of self-report items fort the measurement of lateral preferance. BJ Psichology. 1978; 69: 207-11.
12. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, et al. Assessment of pain. Br J Anaesth. 2008; 101: 17-24.
13. Tutun S, Altin F, Ozgonenel L, Cetin E. Demographic characteristics in patients with knee osteoarthritis and relationship with obesity, age, pain and gender. Istanbul Med J. 2010; 11: 109-12.
14. Ozcakır S. Diz Osteoartriti. İrdesel J, editör. Diz Ağrıları. 1. Baskı. Ankara: Türkiye Klinikleri; 2018: 32-8.
15. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage. 2013; 21: 1145-53.
16. Gunduz H. Pain pathogenesis in osteoarthritis. Turkiye Klinikleri J PM&R-Special Topics. 2008; 1: 28-32.
17. Polat CS, Doğan A, Ozcan DS, Köseoğlu BF, Akselim SK. Is there a possible neuropathic pain component in knee osteoartrhtritis? Arch Rheumatol. 2017; 32: 333-8.
18. Puolakka PAE, Rorarius MGF, Roviola M. Persistent pain following knee arthroplasty. Eur J Anaesthesiol. 2010; 27: 455-60.
19. Kehlet H, Dahl JB. The value of multimodal or balanced analgesia in postoperative pain treatment. Anesth Analg. 1993; 77: 1048-56.
20. Annett M. Left, right hand and brain:right shift theory. Lawrence Erlbaum; London, 1985.
21. Baykal O, Dane S, AkarS, Colak A, Pence S. Relationships between hand preference and eye dominance in normal human subjects. Turkish Journal of Medical Sciences. 1995; 24: 95-7.
22. Gündoğan NU. Hand Choice and Dominant Eye. Türkiye Klinikleri. 2005; 25: 327-28.
23. Symonds LL, Gordon NS, Bixby JC, Mande MM. Right-lateralized pain processing in the human cortex: an FMRI study. J Neurophysiol. 2006; 95: 3823-30.
24. Hecht D. Depression and the hyperactive right hemisphere. Neurosci Res. 2010; 68: 77-87.
25. Ji G, Neugebauer V. Hemispheric lateralization of pain processing by amygdala neurons. J Neurophysiol. 2009; 102: 2253-64.
26. Pauli P, Wiedemann G, Nickola M. Pain sensitivity, cerebral laterality, and negative affect. Pain. 1999; 80: 359-64.
27. Merskey H, Watson GD. The lateralization of pain. Pain. 1979; 7: 271-80.
28. Barroso J, Vigotsky AD, Branco P, Reis AM, Schnitzer TJ, Galhardo V, et al. Brain gray matter abnormalities in osteoarthritis pain: a cross sectional evaluation. Pain 2020; 161: 2167-78.
29. Burrowes SAB, Goloubeva O Keaser ML, Haythornthwaite JA, Seminowicz DA. Differences in gray matter volume in episodic migraine patients with and without prior diagnosis or clinical care. J Headache Pain. 2021; 22: 127.
30. Lin JC, Chu LF, Stringer EA, Baker KS, Sayyid ZN, Sun J, et al. One month of oral morphine decreases gray matter volume in the right amygdala of individuals with low back pain: Confirmation of previously reported magnetic resonance imaging results. Pain Med. 2016; 17: 1497-504.
31. Northon S, Deldar Z, Piche M. Spinal and cerebral integration of noxious inputs in left-handed individuals. Brain Topog. 2021; 34: 568-86.
32. Chandramouli R, Kanchan B, Ambadevi B. Right-left asymmetry in tonic pain perception and its modification by simultaneous contralateral noxious stimulation. Neuropsychologia 1993,31: 687-94.
33. Schiff BB, Gagliese L. The consequences of experimentally induced and chronic unilateral pain: reflections of hemispheric lateralization of emotion. Cortex. 1994; 30: 255-67.
34. Lugo M, Isturiz G, Lara C, Garcia N, Eblen-Zajjur A. Sensory lateralization in pain subjective perception for noxious heat stimulus. Somatosensory Motor Research. 2002; 19: 207-12.
35. Lithwick A, Lev S, Binshtock A. Chronic pain-related remodelling of cerebral cortex - 'pain memory': a possible target for treatment of chronic pain. Pain Management. 2013; 3: 35-45.
36. Yang S, Chang MC. Chronic pain:Structural and functional changes in brain structures and associated negative affective states. Int J Mol Sci. 2019; 20: 3130.

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# Association Between Quality of Life and Sarcopenia Components in Older Adults

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## ABSTRACT

**Introduction:** Sarcopenia is a serious cause of mortality and morbidity. Expressing that the quality of life of older adults may be a sign of sarcopenia. The purpose of this study was to explore the association between the Euro-Quality of Life Visual Analog Scale (EQ-VAS) and sarcopenia components in older adults.

**Methods:** Patients aged over 60 years who visited geriatric outpatients between October 2016 and August 2021 were included in the study. The overall quality of life was evaluated using the EQ-VAS. Handgrip strength (HGS), Chair Stand Test (CST), skeletal muscle mass (SMM), usual gait speed (UGS), and timed up-go test were measured to assess sarcopenia components.

**Results:** A total of 545 patients were included in the study. The median EQ-VAS score was 70 (10-100). Age, UGS, and HGS were found to be statistically significant determinants of the EQ-VAS ($p=0.014$, $p=0.005$, $p<0.001$) after adjusting for gender, diabetes, body mass index, SMM, and CST.

**Conclusion:** Our study suggests that age, UGS, and HGS are associated with self-reported quality of life in older adults. The results highlight the importance of assessing the quality of life of older adults in clinical practice to improve sarcopenia.

**Keywords:** Quality of life, older adults, sarcopenia

## Introduction

The life expectancy of the human population is increasing, leading to a greater prevalence of comorbid conditions in the older adult age group (1). Sarcopenia is a health problem that is commonly associated with other diseases (falls, fractures, disability and even ending of life) in older adults (2).

The Euro-Quality of Life-5D (EQ-5D3L) is a two-part scale based on the assessment of EQ-5D and the EQ-Visual Analog Scale (EQ-VAS) (3). The EQ-VAS is a visual scale based on which participants can express their health status, functionality, and general perception of life (3,4).

A few studies to date have reported an association between sarcopenia and quality of life (5,6). Components of the sarcopenia test, on the other hand, may be impractical due to the large scale of patients and the limited scale of physicians with the ability to take such measurements, the patient's general condition disorder, and balance-vision-hearing problems. In diagnosing sarcopenia in these unsuitable conditions, can a self-reported quality of life score be used as an indicator of sarcopenia? For these reasons, the current study investigated the relationship between sarcopenia components and EQ-VAS in geriatric outpatients.

## Methods

Included in this retrospective cross-sectional designed study were participants over the years of 60 who applied to geriatric outpatients between October 2016 and August 2021. Upon admission to the geriatric outpatients, the patients underwent a comprehensive geriatric evaluation by trained personnel, taking as long as the prevailing conditions permitted, although some patients were extracted from our study due to the unsuitability of their general condition (cognitive problems, hand osteoarthritis, depression, stroke, neuropathy, pacemaker), the absence of trained personnel who were able to perform the tests, time restraints, refusal to give consent, and an inability to evaluate the data with a comprehensive geriatric evaluation. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed in this study (7). Ethics committee consent for the study was obtained from the İstanbul University, İstanbul Faculty of Medicine Ethics Committee (approval number: 09, date: 13.05.2022).

The medical histories of the participants were enrolled retrospectively based on participant file data, and their overall quality of life was evaluated using the EQ-VAS, a VAS in which a score of 0 demonstrated

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the worst health condition and 100 demonstrated the best health condition (3).

The patients' physical activity levels were determined based on their self-reported engagement in physical activity, with the options: never, sometimes, 1-2 days a week, or every day. Height measurements were performed using a stadiometer, while weights and skeletal muscle mass (SMM) were obtained using a bioelectrical impedance device, all in accordance with standard procedures. Body mass index (BMI) was calculated by dividing weight by height$^2$ (8).

Handgrip strength (HGS) was evaluated for the assessment of sarcopenia. Patients who did not meet the HGS extracted criteria were evaluated using a hand-held dynamometer as follows: while seated in an appropriate position, the patients were instructed to squeeze the hand dynamometer as hard as feasible for 2-3 seconds. The measurements were repeated three times for both hands, and the highest recorded value was obtained (2).

Probable sarcopenia was evaluated based on low HGS. Diagnoses of probable sarcopenia were made using the regional cut-off values recommended by the European Working Group on Sarcopenia in Older People (EWGSOP-2) (<35 kg and <20 kg in males and females, respectively) (2,9).

The Chair Stand Test (CST) was used to assess low muscle strength. For the CST measurements, the patients were asked to stand up five times from a sitting position without using their upper extremities, and the time taken was recorded. Usual gait speed (UGS) and timed up go test (TUG) were used to evaluate physical performance. For the UGS, older adults were asked to walk 4 meters (m) at normal speed. A cut-off value of ≤0.8 m/s was defined for a low walking speed (2). In the TUG, patients were asked to get up from their chair, walk 3 meters, and sit down again, and the duration of the activity was recorded. A cut-off of >=20 s was defined for impaired TUG (2).

### Statistical Analysis

SPSS for Windows (Version 15.0. SPSS Inc. (Chicago, IL, USA) was used for statistical analysis. Descriptive statistics of our study results were presented as numbers (percentages) or means + standard deviations or medians (minimum-maximum). The anormal distribution of numerical variables between the two independent groups were made using a Mann-Whitney U test. The associations among the numerical variables were evaluated by a Spearman correlation if the analysis the parametric test condition was not met. The determining determinants were analyzed by regression analysis. The statistical alpha significance level was admitted as $p<0.05$.

## Results

A total of 1,070 older participants aged over 60 years were initially evaluated, and 525 patients were subsequently excluded from the study because they did not meet the criteria. The final model size covered 545 patients, with a median age of 73 (60-93) years. Of the total, n=375 (68.8%) were female and n=178 (32.7%) were diabetic. The median EQ-VAS score was 70 (10-100). The baseline data of the study population are presented in Table 1.

EQ-VAS was positively correlated with UGS, HGS, SMM, and daily physical activity and negatively correlated with age, TUG, BMI, CST, number of drugs, and number of diseases (p=0.034 for age; p=0.033 for BMI; p=0.015 for SMM, p<0.001 for other comparisons) (Table 2).

The EQ-VAS scale score measurements were significantly lower among the female participants than among the male participants and in the groups with impaired UGS, impaired TUG, and probable sarcopenia (gender p=0.012, p<0.001 for other comparisons).

**Table 1. Baseline characteristics of the study population**

| | |
|---|---|
| Age median (min.-max.) | 73 (60-93) |
| **Gender n (%)** | |
| Male | 170 (31.2%) |
| Female | 375 (68.8%) |
| Diabetes n (%) | 178 (32.7%) |
| EQ5D-VAS median (min.-max.) | 70 (10-100) |
| TUG (s) mean ± SD (min.-max.) | 9.1 (5-36) |
| UGS (m/s) median (min.-max.) | 0.95 (0.21-1.60) |
| Impaired UGS n (%) | 141 (25.9%) |
| Impaired TUG n (%) | 30 (5.5%) |
| HGS (kg) median (min.-max.) | 24 (6-52) |
| BMI (kg/m$^2$) median (min.-max.) | 29.7 (15.9-58.8) |
| SMM median (min.-max.) | 24.2 (16-40.5) |
| Probable sarcopenia (35/20 kg) n (%) | 194 (35.6%) |
| CST (s) median (min.-max.) | 11.1 (5,6-66) |
| Number of medication medians (min.-max.) | 2 (0-17) |
| Number of diseases median (min.-max.) | 3 (0-10) |
| **Daily physical activity status (%)** | |
| Never | 66 (12.1%) |
| Sometimes | 11 (2.0%) |
| 1-2 times per week | 188 (34.5%) |
| Every day | 280 (51.4%) |

Data are presented as mean + standard deviation, median (interquartile range), or number (percentage) as applicable. EQ-VAS: Euro Quality of Life Visual Analog Scale, TUG: Timed-up-and-go test, UGS: User's gait speed, HGS: Handgrip strength, BMI: Body mass index, SMM: Skeletal muscle mass, CST: Chair stand test, SD: Standard deviation, min.: Minimum, max.: Maximum

**Table 2. Correlation between EQ5-VAS with related factors**

| **EQ5-VAS** | | |
|---|---|---|
| | **r** | **p** |
| Age | -0.433 | **0.034*** |
| TUG (s) | -0.257 | **<0.001*** |
| UGS (m/s) | 0.265 | **<0.001*** |
| HGS (kg) | 0.254 | **<0.001*** |
| BMI (kg/m$^2$) | -0.091 | **0.033*** |
| SMM | 0.104 | **0.015*** |
| CST (s) | -0.216 | **<0.001*** |
| Number of medications | -0.211 | **<0.001*** |
| Number of diseases | -0.218 | **<0.001*** |
| Daily physical activity status | 0.258 | **<0.001*** |

*Significant p-values. EQ-VAS: Euro Quality of Life Visual Analog Scale, TUG: Timed-up-and-go test, UGS: Usual gait speed, HGS: Handgrip Strength, BMI: Body mass index, SMM: Skeletal muscle mass, CST: Chair stand test

There were no statistically significant differences in the EQ-VAS measurements between patients with and without diabetes (p=0.872) (Table 3).

All factors including age, sex, diabetes, HGS, BMI, SMM, CST, and UGS were subjected to linear regression analysis to determine their effects on EQ-VAS; age (p=0.014), UGS (p=0.005), and HGS (p<0.001) were determined to be statistically significant (Table 4).

## Discussion

In our study examining the relationship between the EQ-VAS scores and the results of the sarcopenia components of 525 older adults living in the community, the factors associated with the EQ-VAS, which is a component of the general quality of life, were age, UGS, and HGS. In addition, the EQ-VAS scores were significantly lower in female members of the groups with impaired UGS, impaired TUG, and probable sarcopenia.

**Table 3. Association between diabetes, sex, probable sarcopenia, and impaired physical performance based on the EQ5D-VAS in univariate analyses**

| EQ5D-VAS | | | |
|---|---|---|---|
| | **Mean ± SD** | **Median (min.-max.)** | **p** |
| **Gender** | | | |
| Male | 67.8±20.0 | 70 (10-100) | 0.012* |
| Female | 63.5±20.0 | 60 (10-100) | |
| **Diabetes** | | | |
| (-) | 65.1±19.7 | 70 (10-100) | 0.872 |
| (+) | 64.2±20.8 | 70 (10-100) | |
| **Impaired UGS** | | | |
| (-) | 66.8±19.5 | 70 (10-100) | <0.001* |
| (+) | 59.0±20.6 | 60 (10-100) | |
| **Impaired TUG** | | | |
| (-) | 65.7±19.7 | 70 (10-100) | <0.001* |
| (+) | 50.3±20.9 | 50 (10-90) | |
| **Probable sarcopenia (35/20 kg)** | | | |
| (-) | 67.6±18.9 | 70 (10-100) | <0.001* |
| (+) | 59.7±21.1 | 60 (10-100) | |

*Significant p-values. EQ-VAS: Euro Quality of Life Visual Analog Scale, TUG: Timed-up-and-go test, UGS: Usual gait speed, SD: Standard deviation, min.: Minimum, max.: Maximum

**Table 4. Regression of the EQ5D-VAS demographics data's of study population and sarcopenia related measures**

| Dependent variable: EQ5D-VAS | | | |
|---|---|---|---|
| | **B** | **Beta** | **p** |
| Age | 0.382 | 0.130 | 0.014* |
| Gender | 4.857 | 0.114 | 0.160 |
| Diabetes | 0.272 | 0.006 | 0.881 |
| UGS (m/sn) | 14.938 | 0.167 | 0.005* |
| HGS (kg) | 0.606 | 0.247 | <0.001* |
| BMI (kg/m$^2$) | -0.166 | -0.048 | 0.432 |
| SMM | -0.069 | -0.015 | 0.858 |
| CST (sn) | -0.152 | -0.043 | 0.403 |

Adjusted R squared value: 0.074. *Significant p-values. EQ-VAS: Euro Quality of Life Visual Analog Scale, TUG: Timed-up-and-go test, UGS: Usual gait speed, HGS: Handgrip strength, BMI: Body mass index, SMM: Skeletal muscle mass, CST: Chair stand test

Many studies have investigated the relationship between UGS and EQ-VAS (6,10-14).

Trombetti et al. (6) conducted a prospective study on 48 older adults, 22 of whom had limited mobility, for 3 years and reported a correlation between decreased UGS and deterioration in general quality of life in both groups of older adults. Similarly, Guralnik et al. (10) examined over 5,000 respondents aged 71 years and over residing in three communities and identified a relationship between low UGS and individual perceptions of general health problems. In a prospective study of 422 participants by Oh et al. (15) examining the effect of lower extremity function and quality of life in older adults, a correlation was found between UGS and the EQ5D index. Perera et al. (11) also reported a relationship between UGS and movement-related aspects of quality of life in a prospective intervention study involving 100 people with limited mobility, 100 who had recovered from a subacute stroke, and 492 community-dwelling older adults. Andersson et al. (13) conducted a study of 360 participants aged over 85 years to explore the relationship between general quality of life and instrumental activities of daily living and found that a low self-reported general quality of life was associated with mobility restriction. In the present study, a significant relationship was identified between UGS and the EO-VAS. This is the first study to report this relationship among older adults in Turkey.

We also investigated the relationship between HGS and SMM based on the EQ-VAS scores in the present study. HGS was found to be related to self-reported general quality of life, whereas SMM had no significant effect. Although our results are compatible with the EWGSOP-2 diagnostic criteria and with studies conducted in other regions reported in the literature, ours is one of the first studies to be conducted in Turkey (2,16,17). The EWGSOP 2 has recently identified muscle strength as more important than muscle mass for the evaluation of sarcopenia, and the fact that HGS and UGS were found to be related in the results of the study supports this (2,18,19).

Lærum-Onsager et al. (5) examined 107 individuals aged 70 years and over with a history of hospitalization and 328 older adults who had not been hospitalized and found that those who were overweight had a lower perception of their general quality of life. Similarly, Goins et al. (20) investigated the relationship between obesity and health-related quality of life in adults aged 65 years and over and reported that older adults with obesity have a lower health-related quality of life. Kim et al. (21) also reported a relationship between obesity and low quality of life in their study, which included 6,057 participants.

You et al. (22) conducted a study on 10,257 community-dwelling individuals over the age of 60 years and found that being underweight was associated with a low general quality of life in both male and female older adults. They further reported that overweight women were more likely to have a low EQ-5D index, whereas overweight men were less likely to have a low EQ-VAS (22).

In the present study, the EQ5D-VAS component was found to be unassociated with BMI, which contrasts with the findings reported in

the literature. The reason for this difference may be ethnic differences or the use of only the EQ5D-VAS.

Furthermore, the EQ-VAS score component of the EQ-5D3L was found to be low in older adults in the present study, which is consistent with the findings of some studies in the literature reporting a tendency for EQ-VAS scores to be low in older adults (7,13).

### Study Limitations

One of the strengths of our study is its status as the first to investigate the relationship between sarcopenia components and self-reported quality of life in a large community sample of older adults in Turkey. Additionally, our study is strengthened by the use of regression analysis to correct for HGS and UGS values in the diagnosis of sarcopenia.

The limitations of our study include its retrospective design, lack of follow-up data, and possible underestimation of the EQ-VAS component, which is common in the literature.

## Conclusion

The results of the present study may be useful for healthcare professionals engaged in the provision of care to the rapidly aging population. Because our society is aging rapidly, the EQ-VAS, which is a simple self-reported assessment tool, can help in cases where UGS and HGS, which are essential components of sarcopenia in older adults, cannot be applied. Further prospective studies are needed to identify any improvement in quality of life after the implementation of the necessary interventions and thus to establish a definitive association between EQ-VAS and UGS.

**Ethics Committee Approval:** Ethics committee consent for the study was obtained from the İstanbul University, İstanbul Faculty of Medicine Ethics Committee (approval number: 09, date: 13.05.2022).

**Informed Consent:** Retrospective study.

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

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## References

1. Beltrán-Sánchez H, Soneji S, Crimmins EM. Past, Present, and Future of Healthy Life Expectancy. Cold Spring Harb Perspect Med. 2015; 5: a025957.
2. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2). Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019; 48: 16-31.
3. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990; 16: 199-208.
4. Machón M, Larrañaga I, Dorronsoro M, Vrotsou K, Vergara I. Health-related quality of life and associated factors in functionally independent older people. BMC Geriatr. 2017; 17: 19.
5. Lærum-Onsager E, Brovold T, Bergland A, Pripp AH, Bye A. Associations between health-related quality of life, body mass index, health status and sociodemographic variables in geriatric patients and non-hospitalized older people: A comparative cross-sectional study. Nutr Health. 2020; 26: 141-50.
6. Trombetti A, Reid KF, Hars M, Herrmann FR, Pasha E, Phillips EM, et al. Age-associated declines in muscle mass, strength, power, and physical performance: impact on fear of falling and quality of life. Osteoporos Int. 2016; 27: 463-71.
7. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007; 335: 806-8.
8. World Health Organization. Obesity and overweight. Fact sheet No 311. 2015. World Health Organisation, 2015.
9. Bahat G, Kilic C, Altinkaynak M, Akif Karan M. Comparison of standard versus population-specific handgrip strength cut-off points in the detection of probable sarcopenia after launch of EWGSOP2. Aging Male. 2020; 23: 1564-9.
10. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994; 49: M85-94.
11. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006; 54: 743-9.
12. Lyu W, Wolinsky FD. The onset of ADL difficulties and changes in health-related quality of life. Health Qual Life Outcomes. 2017; 15: 217.
13. Andersson LB, Marcusson J, Wressle E. Health-related quality of life and activities of daily living in 85-year-olds in Sweden. Health Soc Care Community. 2014; 22: 368-74.
14. Hörder H, Skoog I, Frändin K. Health-related quality of life in relation to walking habits and fitness: a population-based study of 75-year-olds. Qual Life Res. 2013; 22: 1213-23.
15. Oh B, Cho B, Choi HC, Son KY, Park SM, Chun S, et al. The influence of lower-extremity function in elderly individuals' quality of life (QOL): an analysis of the correlation between SPPB and EQ-5D. Arch Gerontol Geriatr. 2014; 58: 278-82.
16. Chan OY, van Houwelingen AH, Gussekloo J, Blom JW, den Elzen WP. Comparison of quadriceps strength and handgrip strength in their association with health outcomes in older adults in primary care. Age (Dordr). 2014; 36: 9714.
17. Silva Neto LS, Karnikowiski MG, Tavares AB, Tavares AB, Lima RM. Association between sarcopenia, sarcopenic obesity, muscle strength and quality of life variables in elderly women. Rev Bras Fisioter. 2012;16:360-367.
18. Curtis E, Litwic A, Cooper C, Dennison E. Determinants of Muscle and Bone Aging. J Cell Physiol. 2015; 230: 2618-25.
19. McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. Longev Healthspan. 2014; 3: 9.
20. Goins RT, Spencer SM, Krummel DA. Effect of obesity on health-related quality of life among Appalachian elderly. South Med J. 2003; 96: 552-7.
21. Kim SR, Kim HN, Song SW. Associations Between Mental Health, Quality of Life, and Obesity/Metabolic Risk Phenotypes. Metab Syndr Relat Disord. 2020; 18: 347-52.
22. You H, Li XL, Jing KZ, Cao HM, Wang J, Bai L, et al. Association between body mass index and health-related quality of life among Chinese elderly-evidence from a community-based study. BMC Public Health. 2018; 18: 1174.

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# Effectiveness of Preoperative Biomarkers: Role of the C-Reactive Protein/Albumin Ratio and Systemic Immune-Inflammation Index in Predicting Acute Cholecystitis Severity

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## ABSTRACT

**Introduction:** The 2018 Tokyo Guidelines are insufficient for preoperative prediction of severe acute cholecystitis (AC) preoperatively. The Parkland Grading Scale (PGS) aids in intraoperative assessment but lacks preoperative utility. Biomarkers like C-reactive protein/albumin ratio (CAR) and systemic immune-inflammation index (SII) were explored for preoperative prediction of severe AC. The present study aimed to investigate the efficacy of biomarkers against severe AC.

**Methods:** A retrospective analysis at the University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital covered patients undergoing early laparoscopic cholecystectomy for AC from January 2014 and January 2023. AC was defined according to the 2018 Tokyo Guidelines criteria. Patients were categorized into two groups based on the PGS for intraoperative findings: Group 1 (grades 1-3) for mild AC and group 2 (grades 4-5) for severe AC. Clinical parameters, intraoperative findings, postoperative outcomes, and biomarkers, including CAR and SII, were analyzed.

**Results:** Of 141 patients, 93 were included in group 1 and 48 in group 2. Group 2 exhibited longer operation times, higher rates of conversion to open cholecystectomy, and complications, and prolonged hospital stays. Clinical parameters such as age, sex, symptom duration, and ASA score were varied between the groups. Biomarkers including C-reactive protein and white blood cell count differed significantly between the groups, with CAR and SII identified as predictive factors for severe AC. The cut-off points were 1.86 for CAR and 1327.69 for SII.

**Conclusion:** Preoperative biomarkers, particularly CAR and SII, can effectively predict severe AC. Levels exceeding 1.86 for CAR and 1327.69 for SII indicate increased conversion to open cholecystectomy and postoperative complication risk.

**Keywords:** Severe acute cholecystitis, C-reactive protein/albumin ratio, systemic immune-inflammation index, Parkland Grading Scale

## Introduction

It is important to accurately evaluate the severity of acute cholecystitis (AC) in patients to improve treatment outcomes and prognosis (1). The Tokyo Guidelines 2018 (TG18) are recommended for evaluating the risk level of patients with AC to determine the most suitable treatment approach. According to the TG18, the diagnostic criteria for AC include duration of symptoms, physical examination findings, laboratory results, such as C-reactive protein (CRP) and white blood cell (WBC) levels, and radiological evaluation. The TG18 uses CRP levels only for diagnosing AC and not as a decisive marker in assessing the severity of AC. The WBC count was used as a criterion for determining disease severity (2). Nevertheless, the 2013 Tokyo Guidelines were found to be insufficient to predict conversion to open cholecystectomy (CC) but sufficient to predict mortality in the literature (3). Additionally, WBC count was not found to predict CC (4). Moreover, there is no difference in the rates of CC and complications between patients undergoing early laparoscopic cholecystectomy, even when the symptom duration exceeds 72 hours (5).

The Parkland Grading Scale (PGS) is based on intraoperative patient observations, and cholecystectomy becomes increasingly challenging from grades 1 to 5 (6). Lee et al. (7) reported that CRP and WBC counts, operation time, intraoperative complications, postoperative complications, and length of hospital stay were all the highest in patients classified as grade 5 on the PGS. In the same study, 87.2% of grade 5 cases on the PGS corresponded to grades 1 and 2 on the TG18. Cripps and Weber (8) found the PGS and the American Association for Surgery of Trauma Grading Scale to be superior to the TG18. They concluded that

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the PGS is the best grading system for AC. However, in the preoperative period, evaluating the severity of AC using PGS is challenging due to its intraoperative nature.

For these reasons, some researchers have turned to biomarkers to assess the severity of AC in the preoperative period. Several studies have identified CRP as a reliable predictor of difficult cholecystectomy or CC (1,9-11). Moreover, various biomarkers, such as procalcitonin, visfatin, and neopterin, have been investigated although their utility is limited (12-14). Biomarkers that are easy to use and inexpensive, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), CRP/albumin ratio (CAR), systemic immune-inflammation index (SII), systemic immune response index (SIRI), prognostic nutritional index (PNI), and Glasgow prognostic score (GPS), have recently been studied. However, conflicting evidence exists regarding the predictive value of these biomarkers in AC and the threshold values that can be used in management (15-27).

The objective of this study was to evaluate the efficacy of preoperative biomarkers for predicting difficult cholecystectomy during early laparoscopic cholecystectomy for AC.

## Methods

We retrospectively analyzed patients who underwent early laparoscopic cholecystectomy for AC at the University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital, Clinic of General Surgery between January 2014 and January 2023. The University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital Local Ethics Committee approved this study (approval number: FSM EAH-KAEK 2023/184, date: 14.12.2023). All participants received written explanations of the study objectives and methods. AC was defined as the presence of at least one feature from each systemic, local, and radiological finding according to the TG18 (2).

### Groups

The characteristics of the gallbladder from the operation notes of the patients included in the study (such as normal gallbladder, adhesion of surrounding tissues to the gallbladder, location of adhesion, hyperemia, pericholecystic fluid, hydrops, grade 1-3 abnormal liver anatomy, intrahepatic gallbladder, Mirizzi syndrome, perforation, and necrosis) were recorded. The grade of each patient was calculated according to the PGS, as defined by Madni et al. (6), based on the intraoperative findings. Patients were classified from 1 to 5. Grades 1, 2, and 3 were grouped into group 1, representing mild cholecystitis and easier cholecystectomy, while grades 4 and 5 were grouped into group 2, indicating severe cholecystitis and more difficult cholecystectomy.

### Clinical Parameters, Intraoperative Findings, and Postoperative Outcomes

Preoperatively, the following information was collected from each patient: Demographic characteristics (age, gender), radiological findings (gallbladder wall thickness, presence of pericholecystic fluid), and clinical findings [severity of AC according to the TG18, American Society of Anesthesiologists (ASA) score]. To ensure the accuracy of the classification (as the groups were established based on mild and severe cholecystitis), intraoperative findings and postoperative results were initially documented. Intraoperative findings included the operation time, type of surgery, and presence of any complications. The postoperative and total hospital stays were documented in the postoperative results.

### Biomarkers

CRP, leukocyte and neutrophil counts, lymphocyte and monocyte counts, platelet and albumin counts, mean platelet volume (MPV), and red cell distribution width (RDW) were recorded for each patient during admission. Subsequently, the following ratios and indices were calculated using the recorded values: NLR, PLR, MLR, CAR, SII, SIRI, PNI, and GPS. SII was calculated by multiplying the monocyte count by the neutrophil count and dividing the result by the lymphocyte count. SIRI was calculated by multiplying the platelet count by the neutrophil count and dividing the result by the lymphocyte count. To calculate PNI, the formula PNI = 10 × albumin (g/dL) + 0.005 × lymphocyte count was used. The GPS was calculated based on CRP and albumin levels. A score of two is assigned if CRP is >10 mg/L and albumin is <3.5 g/dL. A score of one is assigned if only one of these values reaches these levels. A score of 0 was assigned if neither CRP nor albumin meet these levels.

### Statistical Analysis

IBM SPSS 25 software was used for statistical analysis. Means, standard deviations, frequencies, and percentages were used to describe the data. To compare qualitative data between groups, the Pearson's chi-squared test and the Fisher's exact test were employed. The distribution of quantitative data was assessed using the Shapiro-Wilk test. Univariate analysis involved comparing quantitative data between groups using the Student's t-test and the Mann-Whitney U test. Logistic regression analysis was performed to evaluate positive data in the univariate analysis. In logistic regression analysis, statistically significant data were evaluated using the receiver operating characteristic curve (ROC), and the area under the curve (AUC), cut-off points, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were determined. Statistical significance was considered at $p<0.05$.

## Results

Early laparoscopic cholecystectomy for AC was performed in 141 patients. Of these, 93 patients were categorized into group 1 and, while 48 patients into group 2.

### Intraoperative Findings and Postoperative Outcomes

The mean operation time was 71.3±24.45 minutes in group 1 and 102.5±40.55 minutes in group 2 ($p<0.001$). CC was necessary for 1 (1.1%) patient in group 1 and 8 (17%) patients in group 2 ($p=0.001$). Complications were not observed in patients in group 1, whereas 3 patients (6.14%) in group 2 experienced complications ($p=0.038$). Obstructive jaundice resulting from a common bile duct stone was observed in the postoperative period in the first patient, whereas bile leakage from the cystic duct occurred in the remaining two patients. Endoscopic retrograde cholangiopancreatography was performed, and a biliary stent was placed in each of the three patients. The total length of hospital stay was 3.52±2.83 days in group 1 and 6.04±4.24 days in

group 2 (p<0.001). The postoperative hospital stay was 2.22±2.43 days in group 1 and 4.31±3.61 days in group 2 (p<0.001) (Table 1).

### Clinical Parameters

The mean age of patients was 46.6±12.77 years in group 1 and 52.2±16.72 years in group 2 (p=0.027). 60.2% of the patients in group 1 and 37.5% in group 2 were female (p=0.010). The mean symptom duration from symptom onset to admission was 2.15±2.52 days in group 1 and 2.43±2.13 days in group 2 (p=0.064). The mean symptom duration from symptom onset to surgery was 3.46±3.02 days in group 1 and 4.10±2.82 days in group 2 (p=0.037). The mean gallbladder wall thickness on preoperative abdominal ultrasonography was 4.28±1.64 mm in group 1 and 4.51±1.66 mm in group 2 (p=0.441). Pericholecystic fluid was present in 21.5% of patients in group 1 and 45.8% of patients in group 2 (p=0.003). According to the TG18, grade 1 AC was present in 72% of patients in group 1 and 52.1% in group 2, grade 2 AC was present in 26.9% of patients in group 1 and 33.3% in group 2, and grade 3 AC was present in 1.1% of patients in group 1 and 14.6% in group 2 (p=0.001). In group 1, 87% of patients were classified as ASA 1-2 and 13% as ASA 3-4. In group 2, 70.2% of patients were ASA 1-2 and 29.8% were ASA 3-4 (p=0.017) (Table 2).

### Biomarkers

Significant differences were observed between the groups in CRP, WBC count, neutrophil count, lymphocyte count, albumin, NLR, PLR, MLR, CAR, SII, SIRI, PNI, and GPS (p<0.05). However, no statistically significant differences in other biomarkers (platelet count, monocyte count, MPV, and RDW) (p>0.05) (Table 2).

**Table 1. Comparison of intraoperative findings and postoperative outcomes among the study groups**

| | Group 1, (n=93) | Group 2, (n=48) | p-value |
|---|---|---|---|
| Operation time, mean (minute) | 71.3±24.45 | 102.5±40.55 | <0.001[1*] |
| Conversion to open cholecystectomy, n (%) | 1 (1.1) | 8 (16.7) | 0.001[2*] |
| Complication, n (%) | 0 | 3 (6.3) | 0.038[2*] |
| Total hospital stay, mean (days) | 3.52±2.83 | 6.04±4.24 | <0.001[1*] |
| Postoperative hospital stay, mean (days) | 2.22±2.43 | 4.31±3.61 | <0.001[1*] |

[1]Mann-Whitney U test, [2]Fisher's exact test, *p<0.05 significant

**Table 2. Comparison of clinical parameters and biomarkers among the groups in the univariate analysis**

| | Group 1, (n=93) | Group 2, (n=48) | p-value |
|---|---|---|---|
| Age, mean (year) | 46.6±12.77 | 52.2±16.72 | 0.027[1*] |
| **Gender, n (%)** | | | |
| Female | 56 (60.2) | 18 (37.5) | 0.010[2*] |
| Male | 37 (39.8) | 30 (62.5) | |
| **Symptom duration, mean (days)** | | | |
| From onset to admission | 2.15±2.52 | 2.43±2.13 | 0.064[3] |
| From onset to surgery | 3.46±3.02 | 4.10±2.82 | 0.037[3*] |
| **Radiological findings** | | | |
| Gallbladder wall thickness, mean (mm) | 4.28±1.64 | 4.51±1.66 | 0.441[3] |
| Pericholecystic fluid, n (%) | 20 (21.5) | 22 (45.8) | 0.003[2*] |
| **Grade by TG18, n (%)** | | | |
| 1, mild | 67 (72) | 25 (52.1) | 0.001[2*] |
| 2, moderate | 25 (26.9) | 16 (33.3) | |
| 3, severe | 1 (1.1) | 7 (14.6) | |
| **ASA score, n (%)** | | | |
| 1-2 | 80 (87) | 33 (70.2) | 0.017[2*] |
| 3-4 | 12 (13) | 14 (29.8) | |
| **Biomarkers** | | | |
| CRP level, mean (mg/L) | 4.57±6.06 | 13.26±10.57 | <0.001[3*] |
| WBC count, mean (10^3/uL) | 11.93±4.03 | 14.80±5.16 | 0.001[3*] |
| Neutrophil count, mean (10^3/uL) | 8.81±3.67 | 11.93±5.19 | 0.001[3*] |
| Lymphocyte count, mean (10^3/uL) | 2.28±0.86 | 1.88±1.06 | 0.010[3*] |
| Platelet count, mean (10^3/uL) | 270.72±77.66 | 277.66±90.22 | 0.707[3] |
| Monocyte count, mean (10^3/uL) | 0.70±0.32 | 0.83±0.53 | 0.075[3] |
| MPV, mean (fL) | 8.61±1.53 | 8.48±1.66 | 0.659[1] |

**Table 2. Continued**

| | Group 1, (n=93) | Group 2, (n=48) | p-value |
|---|---|---|---|
| RDW (%) | 14.05±1.43 | 14.5±1.48 | 0.051[3] |
| Albumin, mean (g/dL) | 4.31±0.29 | 4±0.59 | 0.003[3*] |
| NLR, mean | 4.5±2.94 | 9.96±6.36 | <0.001[3*] |
| PLR, mean | 131.83±48.97 | 206.01±169.56 | 0.002[3*] |
| MLR, mean | 0.34±0.21 | 0.54±0.41 | 0.005[3*] |
| CAR, mean | 1.07±1.42 | 5.35±12.13 | <0.001[3*] |
| SII, mean | 1172.86±701.48 | 2741.97±3176.0 | <0.001[3*] |
| SIRI, mean | | 4 | 0.001[3*] |
| PNI, mean | 3.31±3.13 | 7.95±9.21 | 0.005[3*] |
| GPS, mean | 38.02±14.27 | 34.23±15.31 | <0.001[3*] |
| | 0.63±0.48 | 1.09±0.53 | |

[1]Student's t-test, [2]Pearson's chi-square test, [3]Mann-Whitney U test, TG18: Tokyo Guidelines 2018, CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, CAR: CRP-albumin ratio, SII: Systemic immune-inflammation index, SIRI: Sysytemic inflammatory response index, PNI: Prognostic Nutritional index, GPS: Glasgow prognostic score, *p<0.05 significant

### Multivariate Analysis and Cut-off Points

Significant clinical parameters and biomarkers in the univariate analysis during the preoperative period were further evaluated by multivariate binary logistic regression analysis. In the multivariate analysis, only CAR and SII were found to be predictive of early laparoscopic cholecystectomy for AC (p<0.05) (Table 3). Subsequently, ROC analysis was conducted for both variables. For CAR, the AUC was 0.780 (p<0.001), the sensitivity was 68.29%, the specificity was 81.71%, the positive predictive value was 65.12%, the negative predictive value was 83.75%, the cut-off point was 1.86, and the accuracy rate was 77.24%. For the SII, the AUC was 0.694 (p<0.001), the sensitivity was 60.42%, the specificity was 75.27%, the positive predictive value was 55.77%, the negative predictive value was 78.65%, the cut-off point was 1327.69, and the accuracy rate was 70.21% (Figure 1).

**Table 3. Predictors of severe acute cholecystitis according to multivariate binary logistic regression analysis**

| | B | S.E. | Wald | p-value | OR | 95% CI |
|---|---|---|---|---|---|---|
| CAR | 0.429 | 0.116 | 13.724 | <0.001* | 1.536 | 1.224-1.928 |
| SII | 0.001 | <0.001 | 6.061 | 0.014* | 1.001 | 1.000-1.001 |

CAR: CRP-albumin ratio, SII: Systemic immune-inlammation index, OR: Odds ratio, CI: Confidence interval, *p<0.05 significant

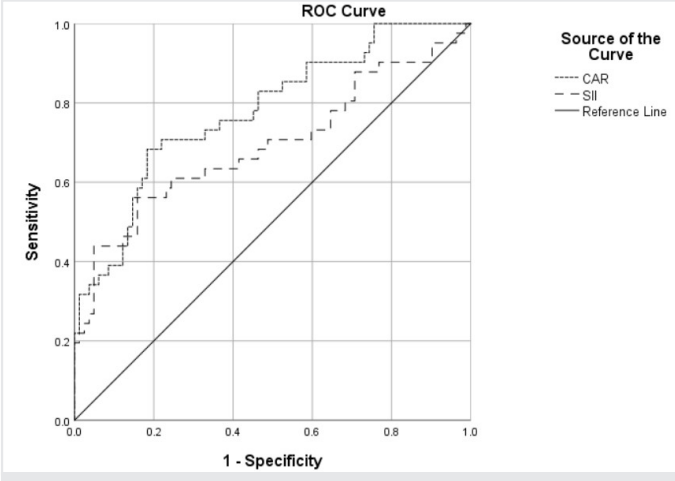


**Figure 1.** ROC curve analyses for CAR and SII
ROC: receiver operating characteristic, CAR: C-reactive protein/albumin ratio, SII: Systemic immune-inflammation index

## Discussion

It is important to understand the severity of AC in the preoperative period. Because the severity of CC increases, the risk of CC and complications increases even in the best medical centers. In this study, we aimed to identify biomarkers that offer easier and a more practical use for preoperative assessment of the severity of AC. Although many studies have investigated biomarkers in the literature, the results have significantly varied. This variance can be attributed to the absence of standardized criteria for defining severe cholecystitis during data grouping and the limited utilization of biomarkers. For these reasons, most studies have biases. To mitigate potential biases, this study focused on accurately grouping patients with AC. To achieve this, we employed the PGS, which is a grading system based on intraoperative characteristics that provides a more comprehensive evaluation of AC severity (8). In our study, the intraoperative and postoperative results were significant in group 2, with longer operative times, more frequent surgical procedures, more complications, and longer hospital stays. These results confirm that PGS grades 4-5 indicate severe cholecystitis.

Furthermore, we included in the study most of the biomarkers used to predict severe cholecystitis in the preoperative period. Through an exhaustive literature review, we identified the most common biomarkers, such as CRP, WBC, neutrophil count, lymphocyte count, platelet count, monocyte count, MPV, RDW, albumin, NLR, PLR, MLR, CAR, SII, SIRI, PNI, and GPS, and included them in our study. As a result, our study identified CAR and SII as predictive factors for severe cholecystitis. CAR emerged as the most predictive factor, with an AUC of 0.780, accompanied by 77.24% AR and a cut-off value of 1.86. Additionally, SII emerged as the second most significant predictive value, with an AUC of 0.694, 70.21% AR, and a cut-off value of 1327.69.

There are limited studies exploring the relationship between AC, CAR, and SII. Three recent studies have reported a relationship between severe AC and CAR (22,25,26). Yilmaz et al. (25) reported an AUC of 0.742 and a cut-off point of 2.61 for CAR. Their study utilized grouping based on the TG18. In contrast, Utsumi et al. (26) found an AUC of 0.78 and a cut-off point of 5.54 for CAR. The grouping was based on laparoscopic cholecystectomy versus CC. However, grouping according to the TG18 in the first study did not compare intraoperative or postoperative outcomes, leaving uncertainty regarding the implications of the results. The TG18 score may not sufficiently denote severe cholecystitis, and it is unclear whether complications or risk escalation correlate with an increased grade. In our study, approximately half of the patients categorized under PGS grades 4-5 exhibited grade 1 AC according to the TG18. In another recent study, Sato et al. (22) found that CAR and NLR were the most effective inflammation-based prognostic scores for predicting grade ≥2 AC as per the TG18. However, the study did not provide insights into CC or complications. In our study, we observed that in group 2, corresponding to the PGS grades 4-5, there were increases in CC, complications, operation time, and hospital stay, with CAR emerging as the most predictive value.

The relationship between AC and SII has been investigated in two recent studies (23,24). Yildiz et al. (24) identified significant associations among NLR, SIRI, and SII. They reported an AUC of 0.742 for the SII using a cut-off point of 790.53. In their studies, the case group comprised patients with AC, and the control group comprised patients who visited the emergency department for any reason with complaints of abdominal pain. Similarly, Serban et al. (23) found that NLR and PLR were also significant, along with SII. They reported an AUC of 0.734 for the SII using a cut-off point of 949.6. Their study involved patients categorized based on intraoperative findings, similar to our study design. Severe AC was associated with prolonged hospitalization, conversion to open cholecystectomy, and increased rate of complications.

In our study, no significant relationship was identified between severe AC and CRP, WBC, albumin, NLR, PLR, MLR, SIRI, PNI, or GPS. Despite this, numerous studies in the literature have linked these biomarkers with severe AC (1,9-11,17-21,27). For instance, in the study conducted by Bouassida et al. (1) categorized patients with gangrenous cholecystitis, pericolic abscess, hepatic abscess, and biliary peritonitis as having advanced AC. Similar to our study, the authors observed a high rate of CC, complications, prolonged hospitalization, and operation time in this group. However, only WBC count, CRP level, and NLR were assessed as biomarkers, with CRP being identified as predictive.

### Study Limitations

Our study has several limitations. First, the sample size is small, which may limit the generalizability of the findings. Second, being a retrospective study, it is susceptible to biases inherent in the study design. However, our study also possesses notable strengths. Specifically, severe AC was accurately defined, enhancing the reliability of our results. Additionally, our study examined the largest number of biomarkers, which contributed to a comprehensive analysis of the condition.

## Conclusion

CAR and SII are the most effective biomarkers of severe AC during the preoperative period. If CAR >1.86 and SII >13.27.69, clinicians should suspect severe AC and anticipate a higher risk of CC and an increased risk of complications.

**Ethics Committee Approval:** The University of Health Sciences Turkey, Fatih Sultan Mehmet Training and Research Hospital Local Ethics Committee approved this study (approval number: FSM EAH-KAEK 2023/184, date: 14.12.2023).

**Informed Consent:** It was obtained.

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

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## References

1. Bouassida M, Zribi S, Krimi B, Laamiri G, Mroua B, Slama H, et al. C-reactive Protein Is the Best Biomarker to Predict Advanced Acute Cholecystitis and Conversion to Open Surgery. A Prospective Cohort Study of 556 Cases. J Gastrointest Surg. 2020; 24: 2766-72.
2. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018; 25: 41-54.
3. Tufo A, Pisano M, Ansaloni L, de Reuver P, van Laarhoven K, Davidson B, et al. Risk Prediction in Acute Calculous Cholecystitis: A Systematic Review and Meta-Analysis of Prognostic Factors and Predictive Models. J Laparoendosc Adv Surg Tech A. 2021; 31: 41-53.
4. Asai K, Watanabe M, Kusachi S, Matsukiyo H, Saito T, Kodama H, et al. Risk factors for difficulty of laparoscopic cholecystectomy in grade II acute cholecystitis according to the Tokyo guidelines 2013. BMC Surg. 2017; 17: 114.
5. Güneş Y, Taşdelen İ, Ergin A, Çakmak A, Bilgili AC, Bayram A, et al. Symptom Duration and Surgeon Volume: Impact on Early Laparoscopic Cholecystectomy for Acute Cholecystitis. Cureus. 2023; 15: e47517.
6. Madni TD, Leshikar DE, Minshall CT, Nakonezny PA, Cornelius CC, Imran JB, et al. The Parkland grading scale for cholecystitis. Am J Surg. 2018; 215: 625-30.
7. Lee W, Jang JY, Cho JK, Hong SC, Jeong CY. Does surgical difficulty relate to severity of acute cholecystitis? Validation of the parkland grading scale based on intraoperative findings. Am J Surg. 2020; 219: 637-41.
8. Cripps MW, Weber NT. Classification Schemes for Acute Cholecystitis. Panam J Trauma Crit Care Emerg Surg. 2022; 11: 139-44.
9. Jessica Mok KW, Goh YL, Howell LE, Date RS. Is C-reactive protein the single most useful predictor of difficult laparoscopic cholecystectomy or its conversion? A pilot study. J Minim Access Surg. 2016; 12: 26-32.
10. Wevers KP, van Westreenen HL, Patijn GA. Laparoscopic cholecystectomy in acute cholecystitis: C-reactive protein level combined with age predicts conversion. Surg Laparosc Endosc Percutan Tech. 2013; 23: 163-6.
11. Díaz-Flores A, Cárdenas-Lailson E, Cuendis-Velázquez A, Rodríguez-Parra A, Trejo-Ávila ME. C-Reactive Protein as a Predictor of Difficult Laparoscopic

Cholecystectomy in Patients with Acute Calculous Cholecystitis: A Multivariate Analysis. J Laparoendosc Adv Surg Tech A. 2017; 27: 1263-8.

12. Park JW, Kim OH, Lee SC, Kim KH, Hong HE, Seo H, et al. Serum level of visfatin can reflect the severity of inflammation in patients with acute cholecystitis. Ann Surg Treat Res. 2020; 99: 26-36.
13. Yaow CYL, Chong RIH, Chan KS, Chia CTW, Shelat VG. Should Procalcitonin Be Included in Acute Cholecystitis Guidelines? A Systematic Review. Medicina (Kaunas). 2023; 59: 805.
14. Nechita VI, Hajjar NA, Drugan C, Cătană CS, Moiș E, Nechita MA, et al. Chitotriosidase and Neopterin as Potential Biomarkers for the Evaluation of Complicated Cholecystitis-A Pilot Study. J Clin Med. 2023; 12: 1641.
15. Akça HŞ, Gürlevik E, Akça MT, Hilal AK. The Role of C-Reactive Protein and Albumin Combined Indexes in Acute Cholecystitis. International Journal of Health Services Research and Policy. 2022; 7: 309-15.
16. Cakcak İE, Kula O. Predictive evaluation of SIRI, SII, PNI, and GPS in cholecystostomy application in patients with acute cholecystitis. Ulus Travma Acil Cerrahi Derg. 2022; 28: 940-6.
17. Karakaş DO, Yeşiltaş M. Validity of the Glasgow prognostic score and modified systemic inflamma-tion score in predicting complicated cholecystitis. Hippokratia. 2020; 24: 15-20.
18. Kartal M, Kalaycı T. Can neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognostic nutrition index, and albumin be used to predict cholecystectomy morbidity in super-elderly patients? Ulus Travma Acil Cerrahi Derg. 2023; 29: 890-6.
19. Lee SK, Lee SC, Park JW, Kim SJ. The utility of the preoperative neutrophil-to-lymphocyte ratio in predicting severe cholecystitis: a retrospective cohort study. BMC Surg. 2014; 14: 100.
20. Mahmood F, Akingboye A, Malam Y, Thakkar M, Jambulingam P. Complicated Acute Cholecystitis: The Role of C-Reactive Protein and Neutrophil-Lymphocyte Ratio as Predictive Markers of Severity. Cureus. 2021; 13: e13592.
21. Micić D, Stanković S, Lalić N, Đukić V, Polovina S. Prognostic Value of Preoperative Neutrophil-to-lymphocyte Ratio for Prediction of Severe Cholecystitis. J Med Biochem. 2018; 37: 121-7.
22. Sato N, Kinoshita A, Imai N, Akasu T, Yokota T, Iwaku A, et al. Inflammation-based prognostic scores predict disease severity in patients with acute cholecystitis. Eur J Gastroenterol Hepatol. 2018; 30: 484-9.
23. Serban D, Stoica PL, Dascalu AM, Bratu DG, Cristea BM, Alius C, et al. The Significance of Preoperative Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Inflammatory Index (SII) in Predicting Severity and Adverse Outcomes in Acute Calculous Cholecystitis. Journal of Clinical Medicine. 2023; 12: 6946.
24. Yildiz G, Selvi F, Bedel C, Zortuk Ö, Korkut M, Mutlucan UO. Systemic inflammation response index and systemic immune inflammation index for predicting acute cholecystitis. Indian Journal of Medical Specialities. 2023; 14: 88-92.
25. Yilmaz S, Aykota MR, Ozgen U, Birsen O, Simsek S, Kabay B. Might simple peripheral blood parameters be an early indicator in the prediction of severity and morbidity of cholecystitis?. Annals of Surgical Treatment and Research. 2023; 104: 332.
26. Utsumi M, Inagaki M, Kitada K, Tokunaga N, Yunoki K, Sakurai Y, et al. C-reactive Protein-to-Albumin ratio predicts conversion from laparoscopic to open cholecystectomy in acute cholecystitis. In Vivo. 2023; 37: 887-93.
27. Beliaev AM, Angelo N, Booth M, Bergin C. Evaluation of neutrophil-to-lymphocyte ratio as a potential biomarker for acute cholecystitis. Journal of Surgical Research. 2017; 209: 93-101.

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# The Role of Quantitative HBsAg Levels in Chronic Hepatitis B Infection

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## ABSTRACT

**Introduction:** Chronic hepatitis B (CHB) infection is essential for patient management, including treatment and follow-up. Therefore, quantitative hepatitis B surface antigen (qHBsAg) may help physicians identify the stages of hepatitis B virus (HBV) infection. This study aimed to examine the variance in qHBsAg levels across various stages of viral infection.

**Methods:** This cross-sectional study, 183 patients who attended the Infectious Diseases outpatient clinic at Haseki Training and Research Hospital between July and December 2020, tested positive for HBsAg, and did not undergo prior treatment.

**Results:** Among the 183 patients, 54.1% were male. The mean qHBsAg level was 2,155 IU/mL (interquartile range: 625-12,759). Correlation analysis revealed that qHBsAg was significantly associated with age, laboratory results, and HBV-DNA. In the receiver operating characteristic analysis, which evaluates the predictive power of qHBsAg for chronic hepatitis, the area under the curve was 0.749, and the optimal cut-off value for qHBsAg was 3,081 IU/mL. The cutoff value for the 95% specificity of qHBsAg in predicting chronic hepatitis was 38,641 IU/mL.

**Conclusion:** Quantitative HBsAg is an easily applicable and relatively inexpensive test for distinguishing different stages of chronic hepatitis. Therefore, qHBsAg can help clinicians assess liver injury and plan treatment at the most appropriate time for patients with CHB infection. In patients with HBV-DNA levels exceeding 2,000 IU/mL, commencement of treatment without the necessity of liver biopsy may be considered when the qHBsAg exceeds 38,000 IU/mL.

**Keywords:** HBeAg, HBV DNA, chronic hepatitis B, qHBsAg, liver biopsy

## Introduction

Hepatitis B virus (HBV) is a member of the Hepadnaviridae family that is characterized by its double-stranded DNA structure (1). Hepatitis B surface antigen (HBsAg) is secreted into the circulation in tubular or spherical forms by hepatocytes infected with the (HBV). Quantitative hepatitis B surface antigen (qHBsAg) levels reflect transcriptional activity originating from closed circular DNA (cccDNA) and integrated DNA within hepatocytes. Therefore, qHBsAg levels can be used as an auxiliary indicator during the course of chronic hepatitis B (CHB) (2).

The standardization of HBsAg quantification has been achieved, leading to an increased utilization of this method in current practice. HBsAg quantification is a valuable parameter that can guide the staging and follow-up of CHB infection and can be used to predict complications of CHB infection and to determine treatment initiation and cessation (3,4).

This finding does not necessarily indicate that patients with infection have CHB. Hence, the identification of individuals with chronic HBV infection and persistent HBV infection holds significant importance in patient management, including treatment decisions and follow-up protocols. In this regard, qHBsAg can help physicians identify the stages of HBV infection (3). The primary objective of this study was to examine variations in qHBsAg levels among distinct infection stages. Additionally, the relationship between qHBsAg and the tested parameters was investigated.

## Methods

### Patients

In this single-center, cross-sectional study, a total of 183 patients with hepatitis B who applied to the Department of Infectious Diseases and Clinical Microbiology, Haseki Training and Research Hospital between July and December 2020 were included.

The inclusion criteria were age 18 years, confirmed HBsAg positivity for a minimum duration of 1 year, and no history of prior HBV treatment.

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The exclusion criteria were coinfection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatocellular carcinoma (HCC), pregnancy, and findings indicative of alcoholic hepatitis.

We recorded the following data for each patient: age, gender, HBsAg, hepatitis B envelop antigen (HBeAg), anti-HBe, HBV-DNA levels, anti-HDV, anti-HCV, anti-HIV, biochemical values such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) total bilirubin, alkaline phosphatase, gamma-glutamyl transferase, albumin, globulin, alpha-feto protein, hemogram, prothrombin time, international normalized ratio values, and abdominal ultrasonography findings. The biopsy findings [fibrosis and histological activity index (HAI)] of patients who underwent liver biopsy within the last 1 year were also recorded.

qHBsAg levels were correlated with biochemical results and HBV-DNA levels obtained concurrently, whereas liver biopsies were performed within 1 year of blood sample collection.

According to the 2017 Classification by the European Association for the Study of the Liver (EASL), patients were categorized into four groups: HBeAg-positive chronic infection (HBV-DNA >10^7 IU/mL, normal ALT); HBeAg-positive chronic hepatitis (HBV-DNA $10^4$-$10^7$ IU/mL, elevated ALT); HBeAg-negative chronic infection (HBV-DNA <2000 IU/mL, normal ALT); and HBeAg-negative chronic hepatitis (HBV-DNA >2000 IU/mL, elevated ALT) (3).

The study was approved by the University of Health Sciences Turkey, Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 2020 -111, date: 08.07.2020).

Informed consent was obtained from the patients prior to their participation in the study.

### Definitions and Reference Ranges

In the present study, biochemical analyses, including serum urea, serum creatinine, AST, and alanine transaminase levels, were performed using kits applied to the Beckman AU2700 auto analyzer devices of the Biochemistry Laboratory of Haseki Training and Research Hospital.

Serological and virological tests were performed using the Abbott Architect I-2000 Device and the Architect Alinity Kit in the microbiology laboratory of Haseki Training and Research Hospital.

For HBsAg quantification, serum samples obtained from patients were stored at 40 °C, and qHBsAg levels were measured using the chemiluminescent microparticle immunoassay technique with the Elecsys HBsAg II (Roche Diagnostics, Indianapolis, USA) kit.

### Statistical Analysis

For statistical analyses, SPSS 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used. The chi-square test was used for categorical variables. Mann-Whitney U test was used for subgroup analyses, and results were interpreted with Bonferroni correction. The Kruskal-Wallis test was used to compare continuous variables between the four groups. The relationships between numerical variables were analyzed using Pearson's correlation analysis when the parametric test conditions were met and Spearman's correlation analysis (Spearman's RHO test) when the parametric test conditions could not be met. Statistical significance was given as $p<0.05$.

Receiver operating characteristic (ROC) analysis was performed with reference to the HAI, fibrosis, and chronic hepatitis classifications, and ROC graphs were used to determine the diagnostic performance of the qHBsAg variable, which is clinically predicted to be effective in determining the risk group. Variables with an area under the curve (AUC) of >0.500 that had a certain sensitivity and specificity for determining chronic hepatitis, HBV-DNA levels, liver fibrosis, and HAI were also calculated.

## Results

A total of 183 patients were included in this study, and 84 (45.9%) were women. The median age of the patients was 40 years (range: 30-48).

Liver needle biopsy was performed in 77 patients within the last 1 year. There were 64 (83.1%) patients with fibrosis between 0 and 2 and 13 (16.9%) with fibrosis 3-4 among patients who underwent biopsy. Fibrosis 5 or 6 was not detected in any patient. A total of 58 (75.3%) patients had HAI between 0-6, and 19 (24.7%) had HAI >6.

According to the hepatitis classification, 13 (7.1%) patients had HBeAg (+) chronic infection, 40 (21.9%) HBeAg (+) chronic hepatitis, 96 (52.5%) HBeAg (-) chronic hepatitis, and 34 (18.6%) were in the HBeAg (-) chronic hepatitis group.

The demographic characteristics and fundamental test outcomes are presented in Table 1.

The comparison of the patient groups in terms of clinical and demographic characteristics, such as sex, age, laboratory results, HBV-DNA, qHBsAg, fibrosis, HAI scores, and hepatosteatosis, are presented in Table 2. Subgroup analyses performed according to Bonferroni correction for these features are presented in Table 3.

In the correlation analysis, qHBsAg was significantly associated with age, ALT, AST, albumin, PTZ, AFP, and HBV-DNA in the general study group. Furthermore, notable correlations were observed between qHBsAg levels and factors such as age, total protein, albumin, and HBV-DNA in HBeAg-positive patients. Similarly, significant associations were identified between qHBsAg and the fallowing variables; age, ALT, and HBV-DNA in HBeAg-negative patients (Table 4).

A moderate positive correlation was detected between qHBsAg and HBV-DNA in the cohort ($r=0.626$, $p<0.001$) and HBeAg (+) group ($r=0.602$, $p<0.001$). A weak positive correlation was detected between qHBsAg and HBV-DNA in HBeAg (-) group ($r=0.375$, $p<0.001$). In HBeAg (+) and HBeAg (-) patient groups, as the HBV-DNA value increased, the qHBsAg value also increased in Table 4.

The ability of qHBsAg to predict fibrosis and HAI in patients with biopsy results was calculated using an ROC curve. In the ROC analysis, in which the predictive power for fibrosis ≥2 was evaluated, qHBsAg was insufficient to evaluate fibrosis ($p>0.086$) (Figure 1).

In the ROC analysis, the AUC for HAI ≥6 was not statistically significant (AUC=0.611, $p=0.15$). The AUC for HAI ≥9 was statistically significant (AUC=0.742, $p=0.008$).

In the ROC analysis performed to predict chronic hepatitis, the AUC for qHBsAg was statistically significant (AUC=0.749, p<0.001). The cut-off point of qHBsAg for determining chronic hepatitis was 3,081 IU/mL. The sensitivity and specificity were 70.3% and specificity 70.6% for qHBsAg ≤3,081 IU/mL. In recognizing chronic hepatitis, the limit value was 38,641 IU/mL with 95% specificity, and the sensitivity was 18% for this value in Figure 2.

In the ROC analysis to evaluate the power of qHBsAg for HBV DNA >2,000 IU/mL in patients, the AUC for HBV-DNA >2,000 IU/mL was statistically significant (AUC=0.790, p<0.001) in Figure 3. For HBV-DNA >2,000 IU/mL, the cutoff value of qHBsAg was 1.924.5 IU/mL. The sensitivity and specificity of qHBsAg 1.924.5 were 72.3% and specificity was 70.4% for qHBsAg ≥1.924.5.

In the ROC analysis performed to evaluate the predictive power of qHBsAg for HBV-DNA >20.000 IU/mL in patients, the AUC was found to be statistically significant (AUC=0.814, p<0.001) in Figure 4. For HBV-DNA >20,000 IU/mL as the reference, the cut-off value for qHBsAg was determined to be 3.081 IU/mL. The sensitivity was 75% and specificity was 71.3% for qHBsAg ≥3,081.

No significant cutoff values were detected for qHBsAg to predict HBV-DNA between 2,000-20,000 IU/mL (AUC=0.475, p=0.615).

**Table 1. Demographic characteristics, laboratory parameters, and liver biopsy findings**

| Characteristics | Median (IQR) |
|---|---|
| Age (years) | 40 (30-48) |
| **Gender** | |
| Female (n, %) | 84 (45.9) |
| Male (n, %) | 99 (54.1) |
| ALT (IU/L) | 28 (19-49) |
| AST (IU/L) | 26 (20-38) |
| Total bilirubin level (mg/dL) | 0.50 (0.40-0.70) |
| Direct bilirubin administration (mg/dL) | 0.10 (0.10-0.14) |
| Total protein (g/dL) | 72.2 (70-75.8) |
| Albumin (g/dL) | 42 (40-45) |
| INR | 1 (0.90-1) |
| Prothrombin time (sec) | 11.2 (11-12) |
| AFP (IU/mL) | 2.83 (1.9-4) |
| **HBeAg** | |
| Positive | 53 (29.0) |
| Negative | 130 (71.0) |
| HBV-DNA (IU/mL) | 5.271 (623-444.240) |
| qHBsAg (IU/mL) | 2.155 (625.1-12.759) |
| **Fibrosis in biopsy specimens** | |
| 0-2 | 57 (74.0) |
| ≥2 | 20 (26.0) |
| **HAI in biopsy specimens** | |
| 0-6 | 48 (62.3) |
| ≥6 | 29 (37.7) |
| **Hepatosteatosis** | |
| Grade-1 | 38 (67.9) |
| Grade-2 | 18 (32.1) |
| HBeAg + Chr. infection | 13 (7.1) |
| HBeAg + Chr. hepatitis | 40 (21.9) |
| HBeAg - Chr. infection | 96 (52.5) |
| HBeAg - Chr. hepatitis | 34 (18.6) |

IQR: Interquartile range, n: number of data, ALT: Alanine aminotransferase, IU/L: International unit/liter, AST: Aspartate aminotransferase, INR: International normalized ratio (international standardized ratio), sec: second, AFP: Alpha fetoprotein, HBeAg: Hepatitis B envelop antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, qHBsAg: Quantitative Hepatitis B surface antigen, HAI: Histologic activity index, Chr. hepatitis: Chronic hepatitis, Chr. infection: Chronic infection

## Discussion

In total, 183 nave patients diagnosed with CHB were evaluated in this study. Upon evaluation of the correlation analyses, a positive association was identified between qHBsAg levels and ALT, HBV-DNA, and HAI. Consequently, we deduced that employing qHBsAg could be efficacious in determining the necessity for treatment initiation and monitoring patient follow-up.

Quantitative HBsAg is a factor affecting the prognosis of the disease, such as HBeAg positivity, HBV-DNA elevation, and genotype. Previous studies have shown that qHBsAg level >1000 IU/mL in HBeAg-negative CHB patients were associated with disease progression and HCC development (5,6). Additionally, the EASL and American Association for the Study of Liver Diseases guidelines stated that the most important determinant of the decision to treatment cessation is HBsAg loss. There is an annual average loss of HBsAg of 0.4-2.3% depending on the stage of liver disease and patient age. Given that most strategies for the functional cure of HBV infection involve combination therapy with nucleos(t)ide analogs, monitoring HBsAg is crucial for assessing response to novel therapeutic approaches. In addition to HBsAg loss, the degree of HBsAg

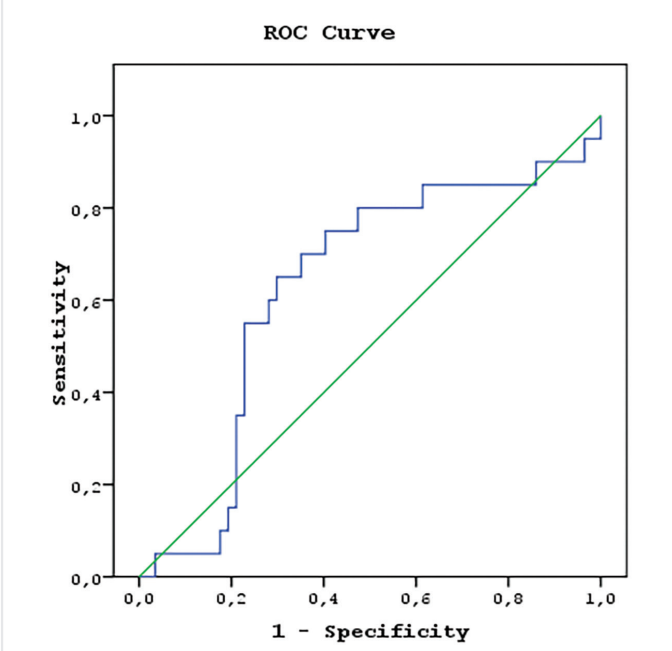


**Figure 1.** Examining the predictor power of qHBsAg Fibrosis 2 and over with the receiver operating characteristic curve

decline or specific cutoff values can serve as secondary endpoints in early clinical trials. However, the precise magnitude of HBsAg reduction or the threshold for treatment success remains uncertain (3,7). This condition is often difficult to achieve and requires long-term treatment. Some studies have examined whether monitoring the qHBsAg level is a predictive value of HBsAg loss during the natural course of the disease. It was concluded that low qHBsAg levels before treatment (<1,000 IU/mL) and a decrease in the early stages of the treatment (e.g. 1-2 log IU/mL) were indicative of the development of HBsAg loss, but the limit value was not determined clearly (5,6).

Many studies on HBsAg quantification have emphasized that qHBsAg measurement is a dynamic parameter that may differ according to the natural course of the disease (8,9). However, it was also shown that qHBsAg can be used as a reference to determine disease severity, evaluate compliance with treatment, and decide whether to terminate

**Table 2. Comparison of clinical and demographic characteristics according to EASL classification**

| Characteristics | HBeAg (+) Chr. infection, (n=13) | HBeAg (+) Chr. hepatitis, (n=40) | HBeAg (–) Chr. infection, (n=96) | HBeAg (–) Chr. hepatitis, (n=34) | p-value |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Female n (%) | 10 (76.9%) | 15 (37.5%) | 51 (53.1%) | 8 (23.5%) | 0.002 |
| Male n (%) | 3 (23.1%) | 25 (62.5%) | 45 (46.9%) | 26 (76.5%) | |
| **Age (years)** | | | | | |
| Median | 26 | 31 | 42 | 40 | <0.001 |
| IQR | 20-31 | 27-47 | 37.25-50.75 | 32-47.25 | |
| **ALT (IU/L)** | | | | | |
| Median | 23 | 62.5 | 20 | 43.5 | <0.001 |
| IQR | 17-29.5 | 43.5-93.5 | 16.25-26 | 33.75-85.75 | |
| **AST (IU/L)** | | | | | |
| Median | 24 | 43.5 | 20 | 36.5 | <0.001 |
| IQR | 19-27.5 | 30.25-62 | 18-25.75 | 27-56 | |
| **Total bilirubin (mg/dL)** | | | | | |
| Median | 0.45 | 0.535 | 0.5 | 0.625 | 0.002 |
| IQR | 0.325-0.525 | 0.4925-0.7875 | 0.4-0.7 | 0.5-0.9 | |
| **Total protein (g/dL)** | | | | | |
| Median | 74.7 | 72 | 72.25 | 72.95 | 0.205 |
| IQR | 68.7-75.9 | 67.9-75 | 69.525-75.175 | 71-77.05 | |
| **Albumin (g/dL)** | | | | | |
| Median | 41 | 40.5 | 43 | 44 | <0.001 |
| IQR | 40-43.5 | 37-43 | 41-45 | 42-46.25 | |
| **INR** | | | | | |
| Median | 0.9 | 0.995 | 0.9 | 1 | 0.048 |
| IQR | 0.9-1 | 0.9-1.1 | 0.9-1 | 0.975-1 | |
| **Prothrombin time (sec)** | | | | | |
| Median | 11.2 | 11.15 | 11.2 | 11.3 | 0.197 |
| IQR | 11.15-12.55 | 11-12.175 | 10.9-11.875 | 11-12.025 | |
| **AFP (IU/mL)** | | | | | |
| Median | 3.41 | 3.275 | 2.525 | 2.575 | 0.092 |
| IQR | 1.33-3.815 | 2.555-4.5375 | 1.9-3.645 | 1.875-4.17 | |
| **HBV-DNA (IU/mL)** | | | | | |
| Median | 146.861 | 20,000,000 | 739.5 | 36.557 | <0.001 |
| IQR | 3.464-92.645.057 | 182.179.8-486.041 | 107-2.921 | 11.893.25-758.476.5 | |
| **qHBsAg (IU/mL)** | | | | | |
| Median | 37.510 | 20.717 | 874.1 | 2.506.5 | <0.001 |
| IQR | 24.742.5-170.410 | 11.789.5-143.825 | 275.325-2.172.25 | 1082.75-6.708.75 | |

EASL: European Association for the Study of the Liver, HBeAg: Hepatitis B envelop antigen, Chr. infection: Chronic infection, Chr. hepatitis: Chronic hepatitis, n: Number of data, IQR: Interquartile range, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IU/L: International unit/liter, qHBsAg: Quantitative hepatitis B surface antigen, INR: International normalized ratio (international standardized ratio), sec: Second, AFP: Alpha fetoprotein, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, qHBsAg: Quantitative hepatitis B surface antigen

treatment (10,11). In this regard, qHBsAg is considered a reliable marker that can be used for patient follow-up.

HBsAg seroclearance and anti-HBs formation are the ultimate targets to be called functional cures and to discontinue treatment in patients who receive such treatments. For this reason, the quantitative measurement of HBsAg level plays an important role in patient follow-up (12). HBsAg seroclearance is an important parameter for predicting decreased HBsAg titers (especially HBsAg <10 IU/mL) and spontaneous HBsAg loss, which is used in treatment follow-up. Other markers reported to be advanced age, low ALT, high platelet, and leukocyte counts (13).

Many studies have reported that quantitative HBsAg can be used to differentiate between chronic infection and hepatitis (8,9). In a study by Brunetto et al. (14), it was reported that a qHBsAg level of 1000 IU/mL is an appropriate limit for differentiating between active and inactive hepatitis B in genotype D patients. In contrast, in our study, the sensitivity was calculated to be 86.5% and specificity 45.9% for qHBsAg 1000 IU/mL in predicting chronic hepatitis. In the present study, the AUC was statistically significant as a result of the qHBsAg level with reference to chronic hepatitis (AUC=0.749) (p<0.001). The cut-off value of qHBsAg for determining chronic hepatitis was 3,081 IU/mL. The sensitivity was calculated as 70.3%, and specificity was 70.6% at this cut-off point. The 95% specificity limit of qHBsAg for recognizing chronic hepatitis was determined to be 38.641 IU/mL. The initiation of antiviral treatment without liver biopsy may be considered because of the high specificity values at this and above the qHBsAg levels.

Different qHBsAg results were found at different disease stages because of the qHBsAg dynamism. In a study conducted in China, in which

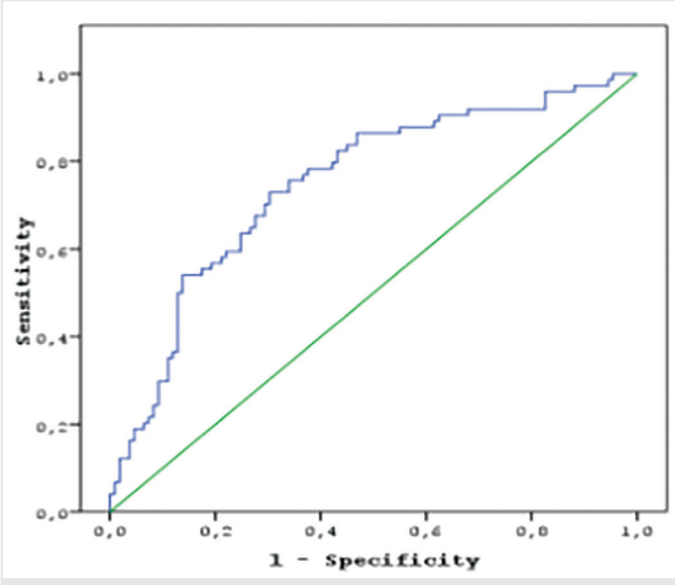


**Figure 2.** Examining the predictor power of qHBsAg for chronic hepatitis with ROC curve

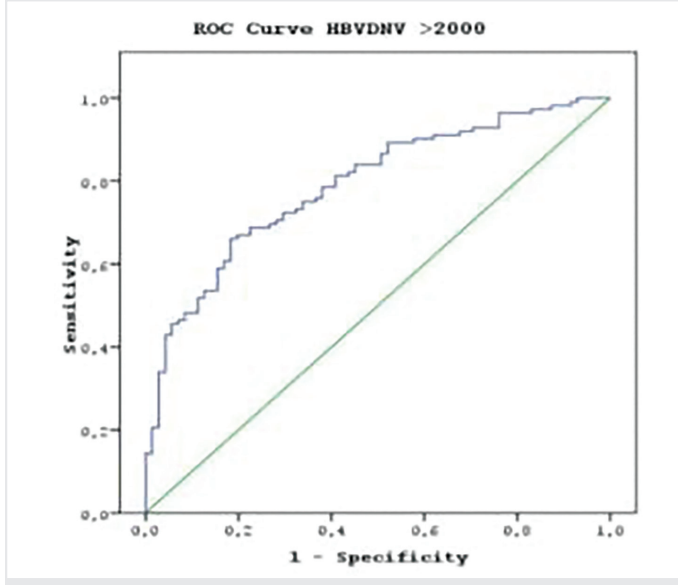


**Figure 3.** Examining the predictor power of qHBsAg for HBV DNA >2.000 IU/Ml using the receiver operating characteristic curve

**Table 3. Subgroup analyses of the clinical and demographic characteristics of the patient groups**

| Characteristics | HBeAg (+) Chr vs. Infection | | HBeAg(+) vs. Chr. Hepatitis | | HBeAg (-) vs. Chr. infection | |
|---|---|---|---|---|---|---|
| | HBeAg (+) Chr. hepatitis | HBeAg (-) Chr. infection | HBeAg (-) Chr. hepatitis | HBeAg (-) Chr. infection | HBeAg (-) Chr. hepatitis | HBeAg (-) Chr. hepatitis |
| | p | p | p | p | p | p |
| Gender | 0.031 | 0.185 | 0.002 | 0.097 | 0.196 | 0.002 |
| Age (years) | 0.006 | <0.001 | 0.001 | 0.001 | 0.252 | 0.084 |
| ALT (IU/L) | <0.001 | 0.381 | <0.001 | <0.001 | 0.045 | <0.001 |
| AST (IU/L) | <0.001 | 0.209 | <0.001 | <0.001 | 0.237 | <0.001 |
| Total bilirubin (mg/dL) | 0.014 | 0.225 | 0.006 | 0.056 | 0.198 | 0.003 |
| Direct bilirubin (mg/dL) | 0.061 | 0.268 | 0.026 | 0.057 | 0.153 | 0.001 |
| Albumin (g/dL) | 0.355 | 0.187 | 0.019 | 0.001 | <0.001 | 0.047 |
| INR | 0.338 | 0.728 | 0.200 | 0.053 | 0.649 | 0.013 |
| HBV-DNA (IU/mL) | 0.077 | <0.001 | 0.739 | <0.001 | <0.001 | <0.001 |
| qHBsAg (IU/mL) | 0.148 | <0.001 | <0.001 | <0.001 | <0.001 | 0.001 |

HBeAg: Hepatitis B envelope antigen, Chr. hepatitis: Chronic hepatitis, Chr. infection: Chronic infection, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IU/L: İnternational unit /liter, INR: International normalized ratio (international standardized ratio), HBV-DNA: Hepatitis B virus deoxyribonucleic acid, qHBsAg: Quantitative hepatitis B surface antigen, Bonferroni correction p<0.0083 (the significance value of p-value was evaluated according to Bonferroni correction)

623 people with different stages of hepatitis B were examined, the patients were evaluated in 5 stages, and the disparities in qHBsAg levels throughout the natural course of the disease were examined. In this study, it was found that median qHBsAg levels differed in each stage of CHB, and statistically significant differences were observed between them (p<0.001). Additionally, HBsAg titers were found to be at the highest level in immune-tolerant patients and lowest in inactive carriers. In addition, serum HBsAg levels were positively and strongly correlated with HBV-DNA in the immune clearance stage (r=0.683, p<0.001) (15). Similarly, in the present study, the qHBsAg median values were found to be different in all four groups, and there was a statistically significant difference between them (p<0.001). Also, similarly, the median value was found to be at the highest level in the HBeAg (+) chronic infection group and the lowest in the HBeAg (-) chronic infection group. In the present study, similarly, the total patient group (r=0.626, p<0.001), HBeAg (+) patient group (r=0.602, p<0.001), and HBeAg (-) patient group (r=0.375, p<0.001) had varying degrees of positive correlations between qHBsAg and HBV DNA. In this regard, qHBsAg can provide us with an idea regarding the natural course of the disease.

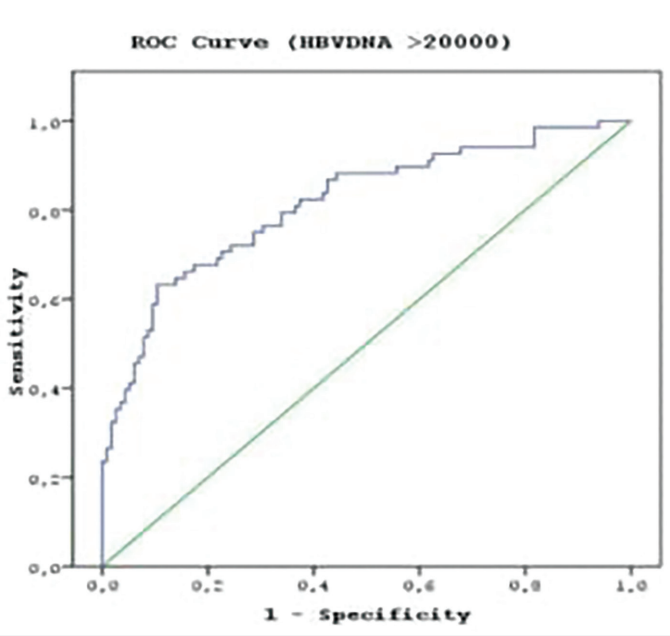


**Figure 4.** Examining the predictor power of qHBsAg for HBV DNA>20.000 IU/Ml using the receiver operating characteristic curve

qHBsAg levels can provide information about disease activation in patients who did not or could not undergo a biopsy. However, the current literature showed that qHBsAg was insufficient for evaluating significant fibrosis. For this reason, non-invasive fibrosis tests (elastography, etc.) can be considered as an alternative to liver biopsy for identifying significant fibrosis.

In several studies conducted in recent years, qHBsAg was shown to be useful in predicting the stage of liver damage (7,16). In a previous investigation, a robust and positive correlation was identified between ALT, HBV-DNA, HAI score, and qHBsAg levels (8). In the present study, as in this study, it was shown that there was a positive correlation between the quantitation of HBsAg in the entire patient group and ALT (p<0.001) and HBV-DNA (p<0.001). These findings may enable the assessment of whether qHBsAg indicates a low or high risk of progressive liver damage, akin to ALT and HBV-DNA levels. In addition, they may offer guidance for physicians in the timing of treatment planning for patients.

The study has some strengths. First, we evaluated a homogenous group of treatment-naive patients. Second, we performed various analysis methods, including correlation and receiver operating characteristic (ROC) curve analysis. Third, we performed HBeAg subgroup analysis.

### Study Limitations

There were several limitations in this study. First, it was conducted at a single center, potentially limiting the generalizability of the findings. Second, the sample size was relatively modest, which may have affected the statistical power and reliability of the findings. Third, liver biopsy

**Table 4. Correlations of quantitative HBsAg levels with other parameters**

| Characteristics | Total | | HBeAg (+) | | HBeAg (-) | |
|---|---|---|---|---|---|---|
| | qHBsAg | | qHBsAg | | qHBsAg | |
| | r | p | r | p | r | p |
| Age | -0.397 | <0.001 | -0.342 | 0.012 | -0.259 | 0.003 |
| ALT (IU/L) | 0.386 | <0.001 | -0.213 | 0.125 | 0.236 | 0.007 |
| AST (IU/L) | 0.354 | <0.001 | -0.208 | 0.135 | 0.151 | 0.086 |
| Total bilirubin (mg/dL) | 0.050 | 0.503 | -0.216 | 0.120 | 0.120 | 0.172 |
| Direct bilirubin (mg/dL) | -0.001 | 0.988 | -0.221 | 0.112 | 0.038 | 0.670 |
| Total protein (g/dL) | 0.021 | 0.780 | 0.300 | 0.029 | 0.060 | 0.498 |
| Albumin (g/dL) | -0.158 | 0.032 | 0.315 | 0.022 | -0.011 | 0.905 |
| INR | 0.106 | 0.153 | -0.133 | 0.341 | 0.119 | 0.177 |
| PT | 0.152 | 0.040 | -0.115 | 0.411 | 0.120 | 0.172 |
| AFP (IU/mL) | 0.155 | 0.036 | 0.058 | 0.681 | 0.110 | 0.212 |
| HBV-DNA (IU/mL) | 0.626 | <0.001 | 0.602 | <0.001 | 0.375 | <0.001 |

HBsAg: Hepatitis B surface antigen, HBeAg: Hepatitis B envelop antigen, qHBsAg: Quantitative hepatitis B surface antigen, r: Correlation coefficient, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IU/L: International unit/liter, INR: International normalized ratio (international standardized ratio), PT: Prothrombin time, AFP: Alpha fetoprotein, HBV-DNA: Hepatitis B virus deoxyribonucleic acid

outcomes were assessed retrospectively over a 1-year period and were not conducted concurrently with other assessments. Additionally, budget constraints prevented genotype determination was not feasible for patients. Finally, the qHBsAg measurements were based on a single assessment, precluding a longitudinal analysis.

## Conclusion

The quantitative HBsAg is an easily applicable and relatively inexpensive test that can be used to differentiate between different stages of CHB. In this respect, qHBsAg may help stratify patients with CHB into chronic infection and hepatitis and manage treatment decision. If the qHBsAg level is >38,000 IU/mL in patients with CHB, treatment initiation may be considered without liver biopsy.

**Ethics Committee Approval:** The study was approved by the University of Health Sciences Turkey, Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 2020 -111, date: 08.07.2020).

**Informed Consent:** Informed consent was obtained from the patients prior to their participation in the study.

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

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

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## References

1. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th Edition 145, 1940-1963.e7
2. Chan HL, Wong VW, Tse AM, Tse CH, Chim AM, Chan HY, et al. Serum hepatitis B surface antigen quantitation can reflect hepatitis B virus in the liver and predict treatment response. Clin Gastroenterol Hepatol. 2007; 5: 1462-8.
3. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017; 67: 370-98.
4. Seto W, Wong DK, Fung J, Huang F, Liu KS, Lai C, et al. Linearized hepatitis B surface antigen and hepatitis B core-related antigen in the natural history of chronic hepatitis B. Clin Microbiol Infect. 2014; 20: 1173-80.
5. Liu J, Yang HI, Lee MH, Lu SN, Jen CL, Wang LY, et al. Incidence and determinants of spontaneous hepatitis B surface antigen seroclearance: a community-based follow-up study. Gastroenterology. 2010; 139: 474-82.
6. Yıldız Kaya S, Mete B, Kaya A, Balkan II, Saltoglu N, Tabak ÖF. The role of quantitative HBsAg in patients with HBV DNA between 2000-20,000 IU/ml. Wien Klin Wochenschr. 2021; 133: 647-53.
7. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018; 67: 1560-99.
8. Chu CM, Liaw YF. HBsAg seroclearance in asymptomatic carriers of high endemic areas: appreciably high rates during a long-term follow-up. Hepatology. 2007; 45: 1187-92.
9. Buti M, Riveiro-Barciela M, Rodríguez-Frías F, Tabernero D, Esteban R. Role of Biomarkers in Guiding Cure of Viral Hepatitis B. Semin Liver Dis. 2020; 40: 49-60.
10. Tseng TC, Liu CJ, Yang HC, Su TH, Wang CC, Chen CL, et al. Determinants of spontaneous surface antigen loss in hepatitis B e antigen-negative patients with a low viral load. Hepatology. 2012; 55: 68-76.
11. Li M, Zhang L, Lu Y, Chen Q, Lu H, Sun F, et al. Early Serum HBsAg Kinetics as Predictor of HBsAg Loss in Patients with HBeAg-Negative Chronic Hepatitis B after Treatment with Pegylated Interferonα-2a. Virol Sin. 2021; 36: 311-20.
12. Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HLA, Chan HL. The role of quantitative hepatitis B surface antigen revisited. J Hepatol. 2017; 66: 398-411.
13. Han ZG, Qie ZH, Qiao WZ. HBsAg spontaneous seroclearance in a cohort of HBeAg-seronegative patients with chronic hepatitis B virus infection. J Med Virol. 2016; 88: 79-85.
14. Brunetto MR, Oliveri F, Colombatto P, Moriconi F, Ciccorossi P, Coco B, et al. Hepatitis B surface antigen serum levels help to distinguish active from inactive hepatitis B virus genotype D carriers. Gastroenterology. 2010; 139: 483-90.
15. Zeng LY, Lian JS, Chen JY, Jia HY, Zhang YM, Xiang DR, et al. Hepatitis B surface antigen levels during natural history of chronic hepatitis B: a Chinese perspective study. World J Gastroenterol. 2014; 20: 9178-84.
16. Tseng TC, Kao JH. Clinical utility of quantitative HBsAg in natural history and nucleos(t)ide analogue treatment of chronic hepatitis B: new trick of old dog. J Gastroenterol. 2013; 48: 13-21.

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# Evaluation of the Clinical Characteristics, Diagnostic Methods, and Long-term Outcomes of Patients with Insulinoma

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## ABSTRACT

**Introduction:** Insulinoma is a rare disease, however the most common cause of hypoglycemia due to excess insulin secretion. Diagnosis and localization can be challenging. This study evaluated the clinical features, diagnostic workup, management, and outcomes of patients with insulinoma.

**Methods:** The records of 13 patients with insulinoma who were followed up at İstanbul University, İstanbul Faculty of Medicine were retrospectively reviewed.

**Results:** The mean age of the 13 patients (female/male: 11/2) was 43.9±12.5 years at diagnosis. The mean tumor diameter was 14.3±6.7 mm and localized at the head in 30.8%, at the tail and/or body in 61.6%, and at both the head and body in 7.6% of patients. The tumor was correctly localized by magnetic resonance imaging in 10/13 patients, $^{68}$Ga DOTATATE positron emission tomography/computed tomography in 4/8, endoscopic ultrasound in 3/7, and selective arterial calcium stimulation in 4/4 patients. Eleven patients were operated. Distal pancreatectomy was performed in 4 patients, distal pancreatectomy plus splenectomy in 3, and enucleation in 4 of the patients. The median follow-up duration was 4 years. In 8 patients, cure was achieved with surgery alone. Somatostatin receptor analog (SSRA) treatment was initiated in 2 cases and one of whom developed lymph node metastasis 2.5 years after surgery under SSRA treatment and she was reoperated. These patients had stable disease at the last visit.

**Conclusion:** Insulinomas are usually small tumors, but they can cause severe symptoms. A multidisciplinary approach is required for diagnosis and treatment. In some patients, different imaging modalities may be necessary for tumor localization.

**Keywords:** Insulinoma, pancreatic neuroendocrine tumor, hyperinsulinemic hypoglycemia

## Introduction

Insulinoma is the most common functioning pancreatic neuroendocrine tumor (PNET) and is a rare disease with an incidence of 0.7-4 cases/million/year (1-4). Most insulinomas are sporadic tumors, but they can also be associated with hereditary syndromes, such as multiple endocrine neoplasia type 1 (MEN1), tuberous sclerosis complex, and neurofibromatosis type 1. More than 90% of insulinomas are benign, approximately 10% are multiple, and 5-10% occur in association with MEN1 syndrome. The risk of recurrence is higher in patients with MEN1 (2,5,6). Tumors originate from the beta cells of the pancreas and are characterized by increased insulin secretion, resulting in hypoglycemia. Hypoglycemia leads to autonomic symptoms, such as tremors, palpitations, diaphoresis, and hunger, as well as neuroglycopenia symptoms, such as confusion, cognitive impairments, visual changes, unusual behavior, memory loss, seizure, and impaired consciousness. Most patients with insulinoma present with Whipple's triad, which includes symptoms of hypoglycemia, documented low plasma glucose levels during symptoms, and symptom relief after carbohydrate ingestion. The diagnosis of insulinoma is delayed because of non-specific symptoms, and some patients are misdiagnosed as having neurological or psychiatric disorders (7).

Insulinoma is characterized by fasting hypoglycemia with inappropriately high insulin and C-peptide levels (hyperinsulinemic hypoglycemia). The diagnostic criteria at the time of symptomatic hypoglycemia (usually glucose level <45 mg/dL) are as follows: C-peptide level >0.6 ng/mL, insulin >3 µU/mL, and beta-hydroxybutyrate <2.7 mmol/L. However, some patients may present with postprandial hypoglycemia. Provocative tests are usually needed for diagnosis; a 72 h fasting test is recommended

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in patients with fasting hypoglycemia (5,8). The differential diagnosis of hyperinsulinemic hypoglycemia includes postbariatric surgery hypoglycemia, nesidioblastosis, autoimmune hypoglycemia, medications, and factitious hypoglycemia. Therefore, a detailed history, physical examination, and laboratory tests are important to determine the etiology (5).

The tumor is located in the pancreas in almost all cases. Non-invasive imaging procedures for tumor localization include computed tomography (CT), magnetic resonance imaging (MRI), $^{68}$Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate positron emission tomography ($^{68}$Ga DOTATATE PET/CT), and fluorine-18-L-dihydroxyphenylalanine PET (18F-DOPA PET). Another non-invasive functional imaging method for benign insulinoma that is not detected by CT/MR is $^{68}$Ga-DOTA-exendin-4 PET/CT. GLP-1 receptors are overexpressed in benign insulinoma; thus, exendin-4 functional imaging is more sensitive (9,10). Invasive procedures include endoscopic ultrasound (EUS) and selective arterial calcium stimulation testing (SACST). EUS can detect small lesions that cannot be localized by non-invasive procedures (11,12).

Treatment options include surgery, non-surgical invasive procedures, and medical therapy. Surgical procedures include tumor removal by enucleation, distal pancreatectomy, and Whipple's operation. EUS-guided radiofrequency ablation is another treatment option for selected patients with localized insulinoma. Diazoxide, calcium channel blockers, and somatostatin receptor ligands are used to inhibit insulin secretion and control symptoms. Liver metastases can be resected or treated by cryoablation, chemoembolization, radioembolization, radiofrequency ablation, and brachytherapy. The treatment of inoperable or more aggressive insulinoma includes debulking surgery, SSRL therapy, everolimus, tyrosine kinase inhibitors, cytotoxic chemotherapy, and peptide receptor radionuclide therapy (5,13,14).

This study aimed to evaluate the clinical characteristics, diagnostic workup, management, and outcomes of patients with insulinoma.

## Methods

This retrospective study included patients diagnosed with insulinoma who were followed up at the Endocrinology and Metabolic Diseases Clinic of İstanbul University, İstanbul Faculty of Medicine between 1986 and 2024. Demographic and clinical characteristics, laboratory results, diagnosis workup, treatment modalities, and treatment outcomes were obtained from the patients' medical records. Cure was defined as the absence of symptoms for at least six months after surgery.

The Ethics Committee of İstanbul University, İstanbul Faculty of Medicine, approved the study protocol (approval number: 02, date: 26/01/2024). Informed consent was not obtained because of the retrospective study design.

### Statistical Analysis

Statistical analyses were performed using SPSS software (version: 21.0). Categorical variables were presented as frequency and percentage of occurrence, whereas numerical variables were presented as median, mean, and standard deviation. The Spearman's test was used for correlation analysis, A p-value of $<0.05$ was considered statistically significant.

## Result

A total of 13 patients with insulinoma were included in this study. There were 11 women (84.6%) and 2 men (15.4%), and the female-to-male ratio were 5.5:1. The mean age at diagnosis was 43.9±12.5 years (median 39, range 28 to 73). The most common symptoms at presentation were confusion (5/13), tremors (4/13), dizziness (4/13), and diaphoresis (3/13). The other symptoms were syncope (2/13), poor memory (2/13), numbness in the hands and feet (2/13), blurred vision (1/13), fatigue (1/13), seizure (1/13), weight gain (1/13), and nightmare (1/13). One patient was misdiagnosed with narcolepsy, and another patient was followed up for a long time with the diagnosis of epilepsy. The median time from initial symptoms to diagnosis was 36 months.

The laboratory results of the patients at the time of admission were as follows: median glucose level, 68 mg/dL (range, 45 to 82), median insulin level 32 µU/mL (range, 5.8 to 201), median C-peptide level, 4.1 ng/mL (range, 1.5 to 15). Symptomatic hypoglycemia developed spontaneously in 6 patients and was detected by a 72-hour fasting test in 7 patients. Blood samples were taken at that time, and the results were as follows: median glucose level, 34 mg/dL (range, 20 to 49), median insulin level 16 µU/mL (range, 3.2 to 277), median C-peptide level, 3.2 ng/mL (range, 1.6 to 14.6). During the 72-hour fasting test, the median time to development of hypoglycemia was 18 hours (2 patients developed within the first 12 hours, 4 patients between 12-24 hours, and 1 patient after 27 hours). Six patients whose cortisol levels were not increased during hypoglycemia were found to have a sufficient cortisol response to the synthetic adrenocorticotrophic hormone stimulation test. HbA1c value of 7 patients was available and the median HbA1c was 4.7%.

One patient had a history of MEN-1-related disease. She had undergone surgery for hyperparathyroidism and Cushing's disease and had a non-functioning adrenal adenoma. Next Generation Sequencing was performed in this case, which revealed a pathogenic mutation in the *Menin* gene (*c.19C>T, p.Gln**).

The diagnostic methods used for tumor localization were as follows: MRI in all patients, $^{68}$Ga DOTATATE PET/CT in 8, EUS in 7, and SACST in 4 patients (Figure 1). The tumor was correctly localized on MRI in 10 patients and on SACST in the remaining 3 patients (Table 1). In 1 of these 3 patients, the results of the $^{68}$Ga DOTATATE PET/CT and SACST were consistent, while in the other 2 patients, the lesions were defined in different places. According to imaging studies, the mean tumor diameter was 17.7±8.9 mm (range, 9 to 35). The tumor was localized at the head in 4 patients (30.8%), at the tail/body in 4 (30.8%), at the tail in 2 (15.4%), at the body in 2 (15.4 %), and at both the head and body in 1 (7.6%) patient.

Eleven of the 13 patients underwent surgery. Distal pancreatectomy was performed in 4 patients, distal pancreatectomy and splenectomy in 3, and enucleation in 4 patients. Two patients were referred to the surgical department for operation (Whipple procedure for one and total pancreatectomy for the other patient) but they discontinued their follow-up.

According to pathological examination results, the mean tumor diameter was 14.3±6.7 mm (median 15 mm), in 8 patients tumor grade was available, and it revealed grades 1 in 2 patients, grade 2 in 5, and grade 3 in 1 patient. The median Ki67 index was 5% (range, 1 to 10) (Table 1).

The median follow-up duration from the first surgery to the last visit was 4 years (range, 2 months to 10 years) in the 11 patients who underwent surgery. In 8 patients, cure was achieved with surgery alone. Somatostatin receptor analog (SSRA) treatment was initiated in cases 8 and 12 after surgery but case 8 developed lymph node metastasis 2.5 years after the first surgery under SSRA treatment, and she was re-operated. These patients had stable disease at the last visit. One patient (case 9) could not be evaluated for remission due to the short postoperative follow-up period.

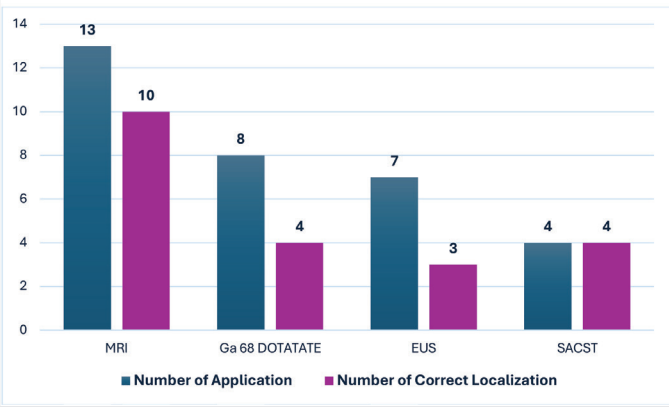


**Figure 1.** Success of invasive and non-invasive imaging methods in localizing the tumor
MRI: Magnetic Resonance Imaging, $^{68}$Ga DOTATATE PET/CT: $^{68}$Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate positron emission tomography, EUS: Endoscopic Ultrasound, SACST: Selective Arterial Calcium Stimulation

Postoperative pancreatic fistula was observed in 2 patients after enucleation (2/4), and diabetes mellitus developed in two patients.

There was a correlation between insulin and C-peptide levels during fasting hypoglycemia and tumor size according to imaging methods (p=0.010; p=0.007, respectively). Furthermore, tumor size on pathological examination was positively correlated with fasting insulin levels and baseline insulin and C-peptide levels and negatively correlated with baseline glucose levels (p=0.010; p=0.022; p=0.003; p=0.008 respectively). Insulin and C-peptide levels during fasting hypoglycemia were positively correlated with baseline levels (Table 2).

## Discussion

In this study, clinical manifestations, laboratory findings, diagnostic methods, localization, and treatment modalities of patients with insulinoma were reviewed and evaluated regarding the success of imaging modalities in the detection of tumors and treatment outcomes in a single center.

Placzkowski et al. (8) reported that the majority of patients with insulinoma were women (57%) and the median age was 50 years. Similarly, Mehrabi et al. (15) showed that insulinoma mostly occurred in the fifth decade of life, and the female-to-male ratio was 1.4:1 (59% female and 41% male). The mean age at diagnosis in our study was compatible with the results of the studies mentioned above. However, female predominance was more prominent, with a female-to-male ratio of 5.5:1 in this study.

**Table 1. Characteristics of patients, localization methods, and treatment modalities**

| Patients | Gender | Age at diagnosis (years) | Duration of symptoms (months) | Diameter of tm (mm) | Localization MRI | Localization $^{68}$Ga DOTATATE | Localization EUS | Localization SACST | Surgery procedure | Pathological examination grade/Ki67% |
|---|---|---|---|---|---|---|---|---|---|---|
| Case 1 | F | 35 | 12 | 11 | Tail | - | - | - | DP | 1% |
| Case 2 | F | 35 | 36 | 18 | Head | - | - | - | E | 4% |
| Case 3 | F | 50 | 36 | 22 | Body | - | - | - | E | Grade 1/2% |
| Case 4 | F | 54 | 36 | 9 | Head | Negative | Head | - | - | - |
| Case 5 | M | 44 | 120 | | Negative | Body | Negative | Distal pancreas | DP | Grade 2/5% |
| Case 6 | F | 30 | 36 | 10 | Body/tail | Negative | Negative | - | DP | Grade 2/7% |
| Case 7 | F | 39 | 12 | 17 | Head* | Head* | Head* | Distal pancreas | DP + S | Grade 2/7% |
| Case 8** | F | 39 | 6 | 23 | Body/tail | Tail | - | Distal pancreas | DP | Grade 1/1% |
| Case 9 | F | 73 | 180 | 30 | Tail | Tail | - | - | DP + S | 3% |
| Case 10 | M | 37 | 48 | 35 | Head-body | - | - | - | - | - |
| Case 11 | F | 51 | 120 | 11 | Head | Head | Head | - | E | Grade 2/5% |
| Case 12 | F | 55 | 18 | | Negative | Head* | Negative | Distal pancreas | DP + S | Grade 2/10% |
| Case 13 | F | 28 | 24 | 10 | Head | - | Head | - | E | Grade 3/10% |

Tm: Tumor, MRI: Magnetic resonance imaging, $^{68}$Ga DOTATATE PET/CT: $^{68}$Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate positron emission tomography, EUS: Endoscopic ultrasound, SACST: Selective arterial calcium stimulation, DP: Distal pancreatectomy, DP + S: Distal pancreatectomy plus splenectomy, *: Suspected, **: Case 8 had multiple tumors associated with MEN-1

**Table 2. Correlation between parameters associated with insulinoma**

| | During fasting hypoglycemia | | | Baseline | | |
|---|---|---|---|---|---|---|
| | Insulin levels | C-peptide levels | Glucose levels | Insulin levels | C-peptide levels | Glucose levels |
| Insulin levels During fasting hypoglycemia, | - | **p<0.001 (CC: 0.988)** | p=0.672 (CC: -0.137) | **p<0.001 (CC: 0.924)** | **p<0.001 (CC:0.882)** | p=0.211 (CC: -0.389) |
| C-peptide levels during fasting hypoglycemia | **p<0.001 (CC: 0.988)** | - | p=0.973 (CC: -0.012) | **p<0.001 (CC: 0.952)** | **p=0.002 (CC: 0.883)** | p=0.382 (CC: -0.311) |
| Glucose levels During fasting hypoglycemia, | p=0.672 (CC: -0.137) | p=0.973 (CC: -0.012) | - | p=0.553 (CC: -0.213) | p=1.000 (CC: 0.001) | p=0.820 (CC: -0.074) |
| Tm diameter* | **p=0.010 (CC: 0.762)** | **p=0.007 (CC: 0.850)** | p=0.894 (CC: -0.049) | p=0.188 (CC: 0.518) | p=0.293 (CC: 0.395) | p=0.866 (CC: -0.061) |
| Tm diameter** | **p=0.010 (CC: 0.797)** | p=0.091 (CC: 0.635) | p=0.567 (CC: -0.221) | **p=0.022 (CC: 0.781)** | **p=0.003 (CC: 0.865)** | **p=0.008 (CC: -0.809)** |
| Age at diagnosis | p=0.470 (CC: 0.231) | p=0.213 (CC: 0.460) | p=0.648 (CC: -0.147) | p=0.590 (CC: 0.195) | p=0.246 (CC: 0.466) | p=0.110 (CC: -0.485) |

Tm: Tumor, CC: Correlation coefficient, * Based on imaging modalities, **: According to pathological examination

The symptoms of insulinoma are non-specific. Therefore, the mean time from symptom onset to diagnosis may range from a few months to several decades. The mean delay between clinical manifestation and diagnosis was reported as 3.6±5.2 years in the study by Hirshberg et al. (16). In our study, the median duration of delay until diagnosis was 3 years, and it was 10 years for the patient with the longest diagnostic delay. A typical finding of insulinoma is fasting hypoglycemia. However, some patients with insulinoma present with hypoglycemia during the postprandial period. Placzkowski et al. (8) reported that 6% of patients presented with symptoms of postprandial hypoglycemia. In our study, hypoglycemia occurred during fasting in all patients.

Complete tumor resection provides remission in insulinoma. However, precise tumor localization is required for surgery. Mehrabi et al. (15) reported that the mean sensitivity of MRI was 57.7%. In our study, MRI was used to identify insulinoma in all patients, and in 10 of 13 patients, the tumor was correctly localized. In a study by Nockel et al. (17), they reported that the tumors were correctly localized in 17 out of 28 (61%) by MRI, and in 9 out of 10 (90%) by $^{68}$Ga DOTATATE PET/CT (17). $^{68}$Ga DOTATATE PET/CT is a sensitive method for detecting PNETs; however, its success in detecting insulinoma may be lower than that in other NETs because of the relatively lower SSTR expression of insulinoma (18). In our study, 8 patients underwent $^{68}$Ga DOTATATE PET/CT imaging. The tumor could be localized in 4 of these 8 patients (50%). Sotoudehmanesh et al. (19) reported that the sensitivity of EUS for insulinoma detection was 92.6% for tumors located in the head of the pancreas, 78.9% for tumors located in the body, and 40.0% for tumors located in the tail. In our study, EUS was performed in seven patients. In 3 of them, the tumor was localized correctly. In the remaining 4 patients, the lesion was located in the distal pancreas and could not be detected by EUS.

In a study by Mehrabi et al. (15), it was shown that the mean tumor size was 16.7 mm (≤20 mm in 83.6% of patients), and the tumor originated from the head and neck in 43.3% of patients, from the tail in 30.9%, and from the body in 25.3%. Similarly, the mean tumor diameter was 14.3±6.7 mm in the study. However, consistent with the observation that beta cells are mostly found in the body and tail of the pancreas, the tumor primarily originated from the body and tail in our patients. Similarly, Sakurai et al. (20) reported that in 73% of patients, tumors originated from the distal pancreas.

Guidelines recommend a first-line surgical strategy for parenchyma-sparing pancreatic resection if technically feasible (5). Sakurai et al. (20) stated that distal pancreatectomy was performed in 32% of the patients, tumor enucleation in 22% patients, and distal pancreatectomy plus tumor enucleation in 8%. In the study of Mehrabi et al. (15), enucleation was the most commonly performed type of surgery (56%) (15). Because most insulinomas were localized in the body or tail of the pancreas, distal pancreatectomy was the most commonly selected procedure (7/11), followed by tumor enucleation (4/11) in our study.

Studies by Placzkowski et al. (8) and Mehrabi et al. (15) showed that 6% of insulinoma were associated with MEN-1. MEN-1 is associated with multiple tumors, a higher rate of malignancy, and recurrence (2). In our study, only 1 patient developed aggressive insulinoma (7.6%), which was associated with MEN-1 syndrome. Mehrabi et al. (15) reported mean cure and recurrence rates of 93% and 7.2% respectively. Recurrence was not observed in our study, and after excluding patients with short-term follow-up, the cure rate after surgery was 80% (8/10). Two patients underwent SSRA treatment and had stable disease (2/10) in our study cohort.

### Study Limitations

The first limitation of our study was the small number of patients due to the low incidence of insulinoma. In addition, given that $^{68}$Ga DOTATATE PET/CT was not performed in all patients, we could not compare the success of imaging methods in localizing the tumors.

## Conclusion

Insulinomas are the most common cause of endogenous hyperinsulinemic hypoglycemia. Management and localization can be challenging despite teamwork. Parenchyma-sparing surgery is recommended for patients with localized insulinoma. Furthermore, in case of a history and/or symptoms associated with MEN 1 syndrome, the patient should be referred for genetic evaluation.

**Ethics Committee Approval:** The Ethics Committee of İstanbul University, İstanbul Faculty of Medicine, approved the study protocol (approval number: 02, date: 26/01/2024).

**Informed Consent:** Informed consent was not obtained because of the retrospective study design.

**Authorship Contributions:** Surgical and Medical Practices - H.H., Ş.G., Ü.M., E.G.I., Y.İ., N.A., G.Y.Y., N.G., A.K.Ü., Ö.S.S.; Concept - H.H., Ş.G., G.Y.Y., N.G., A.K.Ü., Ö.S.S.; Design - H.H., Ş.G., Ü.M., E.G.I., Y.İ., N.A., G.Y.Y., N.G., A.K.Ü., Ö.S.S.; Data Collection or Processing - H.H., Ş.G., Ü.M., E.G.I., Y.İ., N.A., G.Y.Y., N.G., A.K.Ü., Ö.S.S.; Analysis or Interpretation - H.H., Ş.G., Ü.M., E.G.I., Y.İ., N.A., G.Y.Y., N.G., A.K.Ü., Ö.S.S.; Literature Search - H.H., Ş.G., G.Y.Y., N.G., A.K.Ü., Ö.S.S.; Writing - H.H., Ş.G., Ü.M., E.G.I., Y.İ., N.A., G.Y.Y., N.G., A.K.Ü., Ö.S.S.

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## References

1. Cullen RM, Ong CE. Insulinoma in Auckland 1970-1985. N Z Med J. 1987; 100: 560-2.
2. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc. 1991; 66: 711-9.
3. Svensson E, Muth A, Hedenström P, Ragnarsson O. The incidence of insulinoma in Western Sweden between 2002 and 2019. Ann Gastroenterol. 2022; 35: 434-40.
4. Kurakawa KI, Okada A, Manaka K, Konishi T, Jo T, Ono S, et al. Clinical Characteristics and Incidences of Benign and Malignant Insulinoma Using a National Inpatient Database in Japan. J Clin Endocrinol Metab. 2021; 106: 3477-86.
5. Hofland J, Falconi M, Christ E, Castaño JP, Faggiano A, Lamarca A, et al. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. J Neuroendocrinol. 2023; 35: e13318.
6. Marini F, Giusti F, Brandi ML. Genetic disorders and insulinoma/glucagonoma. Endocr Relat Cancer. 2024; 31: e230245.
7. Service FJ, Dale AJ, Elveback LR, Jiang NS. Insulinoma: clinical and diagnostic features of 60 consecutive cases. Mayo Clin Proc. 1976; 51: 417-29.
8. Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, et al. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. J Clin Endocrinol Metab. 2009; 94: 1069-73.
9. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. Eur J Nucl Med Mol Imaging. 2003; 30: 781-93.
10. Sidrak MMA, De Feo MS, Corica F, Gorica J, Conte M, Filippi L, et al. Role of Exendin-4 Functional Imaging in Diagnosis of Insulinoma: A Systematic Review. Life (Basel). 2023; 13: 989.
11. Rösch T, Lightdale CJ, Botet JF, Boyce GA, Sivak MV Jr, Yasuda K, et al. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. N Engl J Med. 1992; 326: 1721-6.
12. Antwi K, Fani M, Heye T, Nicolas G, Rottenburger C, Kaul F, et al. Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study. Eur J Nucl Med Mol Imaging. 2018; 45: 2318-27.
13. Partelli S, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, et al. ENETS consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. Neuroendocrinology. 2017; 105: 255-65
14. Hofland J, Refardt JC, Feelders RA, Christ E, de Herder WW. Approach to the Patient: Insulinoma. J Clin Endocrinol Metab. 2024; 109: 1109-18.
15. Mehrabi A, Fischer L, Hafezi M, Dirlewanger A, Grenacher L, Diener MK, et al. A systematic review of localization, surgical treatment options, and outcome of insulinoma. Pancreas. 2014; 43: 675-86.
16. Hirshberg B, Livi A, Bartlett DL, Libutti SK, Alexander HR, Doppman JL, et al. Forty-eight-hour fast: the diagnostic test for insulinoma. J Clin Endocrinol Metab. 2000; 85: 3222-6.
17. Nockel P, Babic B, Millo C, Herscovitch P, Patel D, Nilubol N, et al. Localization of Insulinoma Using 68Ga-DOTATATE PET/CT Scan. J Clin Endocrinol Metab. 2017; 102: 195-9.
18. Sharma P, Arora S, Karunanithi S, Khadgawat R, Durgapal P, Sharma R, et al. Somatostatin receptor based PET/CT imaging with 68Ga-DOTA-Nal3-octreotide for localization of clinically and biochemically suspected insulinoma. Q J Nucl Med Mol Imaging. 2016; 60: 69-76.
19. Sotoudehmanesh R, Hedayat A, Shirazian N, Shahraeeni S, Ainechi S, Zeinali F, et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. Endocrine. 2007; 31: 238-41.
20. Sakurai A, Yamazaki M, Suzuki S, Fukushima T, Imai T, Kikumori T, et al. Clinical features of insulinoma in patients with multiple endocrine neoplasia type 1: analysis of the database of the MEN Consortium of Japan. Endocr J. 2012; 59: 859-66.

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# Impact of Eltrombopag Therapy in Different Lines of Treatment on Response in Patients with Immune Thrombocytopenia

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## ABSTRACT

**Introduction:** This study aimed to evaluate the results obtained with the preference of eltrombopag according to the line of treatment in patients diagnosed with ITP.

**Methods:** This retrospective study included 51 patients who were treated with eltrombopag for chronic ITP at 3 different centers. Diagnosis of ITP was based on the current literature.

**Results:** Thirty patients (58.8%) received eltrombopag as second-line treatment, 16 patients (31.4%) as third-line, 3 patients (5.9%) as fourth-line treatment, and 2 patients (3.9%) as fifth-line treatment. Twenty-four out of 30 patients (80%) who received eltrombopag as second-line therapy and 12 out of 16 patients who received eltrombopag as third-line therapy demonstrated durable response with no further treatment requirements. Eltrombopag treatment in the second or third line did not affect treatment outcomes (p=0.72).

**Conclusion:** Eltrombopag in the second or third line of treatment did not have a significant effect on treatment response. The earlier line choice of eltrombopag, duration, and possibility of sustained response should be taken into consideration. The lack of a significant relationship between the line of treatment and response to eltrombopag as a TPO-RA should be considered encouraging in terms of long-term follow-up.

**Keywords:** Eltrombopag, immune thrombocytopenia, treatment

## Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts originating from anti-platelet autoantibodies. For the diagnosis of ITP, the elimination of other comorbidities that may cause thrombocytopenia should be ruled out (1). ITP is usually managed with immunosuppressive agents. Corticosteroids represent the first line of choice; prednisone (1 mg/kg/day) with gradual tapering or dexamethasone (40 mg/day) for 4 days are usually preferred glucocorticoid regimens and recommended as the initial choice (2). Several cases of ITP do not maintain sustained remission after the initial therapy and require second-line regimen (3). The choice of second-line treatment options, including rituximab, splenectomy, and thrombopoietin receptor agonists (TPO-RAs), depended on the duration of response to first-line treatment, patient age and request, and accessibility.

Eltrombopag, a member of TPO-RAs, binds to the juxtamembrane domain of the thrombopoietin receptor and induces megakaryocyte proliferation, differentiation, and platelet production through the JAK/STAT, AKT, and MAPK pathways (2,4). Although steroids and intravenous immunoglobulins are effective in obtaining a response in a short time, with rapid effects during the course of ITP; their role in the later phases of the disease is controversial (6). Several studies have demonstrated the effect of eltrombopag in patients with steroid-refractory ITP (2,4).

Although the role of eltrombopag in the second-line treatment of ITP is solid, there are insufficient data regarding response rates with the use of TPO-RAs in later lines. The main aim of our study was to evaluate the results obtained with the preference of eltrombopag according to the line of treatment in patients diagnosed with ITP.

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## Methods

In this retrospective study, 51 patients who were treated with eltrombopag for chronic ITP at 3 different centers were included. The diagnosis of ITP was based on the current literature (7). Diagnosis requires isolated thrombocytopenia (<100,000/mm$^3$) without another known comorbidity or underlying pathologies. Patients aged 18 years and above, diagnosed with ITP for more than 6 months, with a baseline platelet count of 30,000/mm$^3$, and who relapsed after one or more previous treatments were eligible for TPO-RA use.

Patients' demographic data (age and gender), bleeding score for ITP, laboratory results, such as white blood cell, platelet, neutrophil, and lymphocyte counts, hemoglobin level at the time of splenectomy or beginning of eltrombopag, and dates of diagnosis were recorded. The ITP bleeding score was calculated based on the bleeding scale of the World Health Organization. Patients were classified according to the five-point Likert scale as follows: 0, no bleeding; 1, mild blood loss; 2, gross blood loss; and 3, debilitating blood loss with a score of 4 (8).

Responses were classified as follows: Complete response with a platelet count >100,000/mm$^3$, partial response with a platelet count between 30,000 and 100,000/mm$^3$ with at least a 2-fold increase in the initial platelet count, and no response with a platelet count of <30/mm$^3$.

The minimum dose of eltrombopag that ensured a platelet count of >50,000/mm$^3$ was used for the patients. The treatment dose was increased by 25 mg in patients with a platelet count of <50,000/mm$^3$. Eltrombopag dosage was decreased by 25 mg in patients with a platelet count of >150,000/mm$^3$ and discontinued in patients with a platelet count of >250,000/mm$^3$. Other treatment options were considered in patients who did not respond to a maximum of 75 mg of therapy.

This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinical Research Ethics Committee (approval number: 18, date: 27.01.2023).

### Statistical Analysis

Data were analyzed using the SPSS 24 package. program. The mean and standard deviation, median, minimum, and maximum values of the features, frequency, and percentage values were used to identify categorical variables. Mann-Whitney U test was used to evaluate the effect of initial platelet count on treatment with eltrombopag. Pearson's chi-square test was used to compare categorical variables. Fisher's exact test was preferred for small frequencies. The statistical significance level of the data was given as $p<0.05$.

## Results

The patient characteristics are summarized in Table 1. The median age of the patients was 52.3 years (range, 19-84) with 29 women and 22 men. The median number of white blood cells was 9,293/mm$^3$ (range, 4290-25,480), hemoglobin was 12.6 g/dL (range, 6-16.5) and platelet count was 14,000/mm$^3$ (range, 0-43,000). Thirty-two patients (62.7%) underwent bone marrow biopsy during diagnosis or follow-up. Among the 17 patients (33.3%) who presented with bleeding. Forty-six patients (90.2%) received methylprednisolone and 5 patients (9.8%) received dexamethasone as first-line treatment.

Thirty patients (58.8%) received eltrombopag as second-line treatment, 16 patients (31.4%) as third-line, 3 patients (5.9%) as fourth-line treatment, and 2 patients (3.9%) as fifth-line treatment.

Twenty-four out of 30 patients (80%) who received eltrombopag as second-line therapy and 12 out of 16 patients who received eltrombopag as third-line therapy demonstrated durable response with no further treatment requirements. Eltrombopag treatment in the second or third line did not affect treatment outcomes ($p=0.72$). There were no significant differences between these two groups in terms of age, gender, platelet count, white blood cell count, and hemoglobin levels (0.5, 0.76, 0.5, 0.76, 0.8) (Table 2).

Treatment responses were obtained in all 3 patients who received eltrombopag in the fourth line and in one of the 2 patients who received it in the fifth line.

## Discussion

Among the patients included in our study, 30 (58.8%) were in the second, 16 (31.4%) in the third, 3 (5.9%) in the fourth, and 2 (3.9%) in the fifth line of treatment. Our results revealed that the use of eltrombopag in the second or third line of treatment did not have a significant

**Table 1. Baseline characteristics of patients**

| | |
|---|---|
| **Sex, n (%)** | |
| Female | 29 (56.9) |
| Male | 22 (43.1) |
| Age, year (median) | 52.3 (19-84) |
| White blood cell count at diagnosis, median (mm$^3$) | 9,293 (4,290-25,480) |
| Hemoglobin level at diagnosis, median (g/dL) | 12.6 (6-16.5) |
| Platelet count at diagnosis, median (mm$^3$) | 14,000 (0-43,000) |
| **Bone marrow aspiration biopsy, n (%)** | |
| Yes | 32 (62.7) |
| No | 19 (37.3) |
| **Bleeding at diagnosis, n (%)** | |
| Yes | 17 (33.3) |
| No | 34 (66.7) |
| **1. Line treatment rate, n (%)** | |
| Methylprednisolone | 46 (90.2) |
| Dexamethasone | 5 (9.8) |
| **2. Line treatment rate, n (%)** | |
| Eltrombopag | 30 (8.8) |
| Azothiopurine | 2 (3.9) |
| Splenectomy | 8 (15.7) |
| Rituximab | 9 (17.6) |
| Cyclophosphamide | 1 (2) |
| Vincristine | 1 (2) |
| **Eltrombobag step, n (%)** | |
| 2 | 30 (58.8) |
| 3 | 16 (31.4) |
| 4 | 3 (5.9) |
| 5 | 2 (3.9) |

**Tablo 2. Comparison of patients who received eltrombopag between lines 2 and 3**

| | Eltrombopag in the 2nd step, (n=30) | Eltrombopag in the 3rd step, (n=16) | p-value |
|---|---|---|---|
| Response to treatment, n (%) | 24 (80) | 12 (75) | 0.72 |
| White blood cell count, median ($mm^3$) | 7,525 (4,290-25,480) | 9425 (5,900-19,200) | 0.76 |
| Age, year (median) | 52 (19-84) | 49 (27-80) | 0.496 |
| Hemoglobin, median (g/dL) | 13.2 (6-16.5) | 13.3 (7.50-16.30) | 0.818 |
| **Sex** | | | |
| Female | 17 (56.7) | 8 (50) | 0,76 |
| Male | 13 (43.3) | 8 (50) | |
| Platelet | 14,500 (0-43,000) | 11,500 (1,000-35,000) | 0.496 |

effect on treatment response. A serious debate exists on ITP and its treatment algorithm, continues and the early use of TPO-Ras, including eltrombopag, is an important area of research.

A study conducted in 2021 compared the effectiveness and toxicity of splenectomy and eltrombopag as second-line treatment options in 38 patients who underwent splenectomy and 47 patients who underwent eltrombopag. Time to response was significantly shorter with splenectomy than with eltrombopag (p=0.001), but no difference was found between the two arms in terms of overall and 2-year response rates (9). In this meta-analysis including a total of 1202 patients with ITP, the effectiveness and safety of second and subsequent lines of treatment were evaluated. Romiplostim was found to be the most suitable treatment option, followed by avatrombopag, eltrombopag, fostamatinib, and rituximab. The early response rate of romiplostim (platelet count ≥50,000/$mm^3$ at week 2 after initiation of treatment) was superior to avatrombopag, and no significant difference was observed in terms of serious side effects (10). It seems that long-term follow-up, response, and side effects were evaluated in terms of preference for 2nd or other lines of treatment, but there is no sufficient data on the difference in treatment preference between lines of treatment.

Cuker et al. (11) compared patients who received second-line treatment, including eltrombopag, romiplostim, rituximab, splenectomy, and other immunosuppressive agents, within 3 months after the diagnosis with patients who only received first-line treatment. The authors observed that early second-line treatment was used in more severe patients and that corticosteroid use was reduced. In this study, platelet levels improved and bleeding events decreased in all treatment arms; however, the relative platelet increase was lower in those who did not receive early second-line treatment (11). The use of TPO-RAs in patients in the early stages or those with a history of more serious or frequent bleeding is an important area of research and addresses many clinical questions. The findings of our study revealed that the use of eltrombopag in the second or third line of treatment did not have a statistically significant effect on treatment response. It should be taken into consideration that adding eltrombopag into earlier lines of treatment, especially in patients with severe or frequent bleeding events, will help prevent severe bleeding and achieve safe platelet levels. Eltrombopag should be considered an important treatment option in any line of treatment, especially in the presence or history of major bleeding.

Discontinuation of treatment and sustained response after TPO-RA use is reported in 10-30% of patients (12,13). In a study evaluating a total of 260 patients with ITP, 49 patients were examined after discontinuation of eltrombopag, and 26 showed a sustained response without the need for any immunosuppressive agent (14). The median follow-up period was 9 months (range, 6-25 months), the median number of lines of treatment was 4, and 42% of the lines were splenectomized (15). In another study, TPO-RA was discontinued in 20 of 28 patients with complete response; sustained response was achieved in 8 patients (median: 13 months (range, 5-27) (11). Another study examined treatment discontinuation in a total of 31 patients diagnosed with chronic ITP who achieved durable responses with TPO-RA; a sustained response was observed in 9 patients without the need for additional immunosuppressive therapy (15). Of the 9 patients included in the study, 6 had a sustained response after romiplostim and 3 after eltrombopag; all patients were diagnosed with ITP with a median age of 7.8 years, had a median of 4 lines of treatment, and 8 of them were splenectomized (15). In another retrospective study, a total of 53 patients were analyzed, and there was no significant difference in any of the subgroups depending on age, sex, duration of disease, number of prior lines of treatment, splenectomy, or baseline platelet count (16). The fact that the use of eltrombopag in the 2nd or 3rd line of treatment did not have a significant effect on treatment response in our study, when evaluated together with the studies in the literature, may encourage the use of eltrombopag, especially in the early stages. It can also be considered an advantage when considering the sustained response rates.

### Study Limitations

There are important limitations in our study. The limited number of patients was the most significant limitation. Therefore, it was not possible to conduct detailed subgroup analyses.

## Conclusion

In conclusion, in our study, 30 of patients (58.8%) were in the second, 16 (31.4%) in the third, 3 (5.9%) in the fourth, and 2 (3.9%) in the fifth line of treatment. The use of eltrombopag in the second or third line of treatment did not have a significant effect on treatment response. Early line selection for eltrombopag, duration, and possibility of sustained response should be taken into consideration. The lack of a significant relationship between the line of treatment and response to

eltrombopag as a TPO-RA should be considered encouraging in terms of long-term follow-up.

**Ethics Committee Approval:** This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinical Research Ethics Committee (approval number: 18, date: 27.01.2023).

**Informed Consent:** Retrospective study.

**Authorship Contributions:** Surgical and Medical Practices - A.K., V.C.Ç., I.S., R.E.; Concept - A.K.; Design - V.C.Ç., I.S.; Data Collection or Processing - A.K., V.C.Ç.; Analysis or Interpretation - A.K., R.E.; Literature Search - V.C.Ç., I.S.; Writing - A.K., V.C.Ç., I.S., R.E.

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## References

1. Justiz Vaillant AA, Gupta N. ITP-Immune Thrombocytopenic Purpura. 2024 May 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–.
2. Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019; 3: 3829-66.
3. George JN. Sequence of treatments for adults with primary immune thrombocytopenia. Am J Hematol. 2012; 87 Suppl 1: S12-5.
4. de Barros Torelli DFH, Oliveira CBS, Nai GA, Trindade EM, Prestes-Carneiro LE. Eltrombopag for Adults and Children with Immune-Refractory Thrombocytopenic Purpura: A Systematic Review. J Clin Med. 2023; 12: 3872.
5. Wang B, Nichol JL, Sullivan JT. Pharmacodynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand. Clin Pharmacol Ther. 2004; 76: 628-38.
6. Rodeghiero F. Recent progress in ITP treatment. International Journal of Hematology. 2023; 117: 316-30.
7. Provan D, Arnold DM, Bussel JB, Chong BH, Cooper N, Gernsheimer T, ET AL. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019; 3: 3780-817.
8. Fogarty PF, Tarantino MD, Brainsky A, Signorovitch J, Grotzinger KM. Selective validation of the WHO Bleeding Scale in patients with chronic immune thrombocytopenia. Curr Med Res Opin. 2012; 28: 79-87.
9. Uğur MC, Namdaroğlu S, Doğan EE, Turan Erkek E, Nizam N, Eren R, et al. Comparison of Splenectomy and Eltrombopag Treatment in the Second-Line Treatment of Immune Thrombocytopenic Purpura. Turk J Haematol. 2021; 38: 181-7.
10. Yang R, Lin L, Yao H, Ji O, Shen Q. Therapeutic options for adult patients with previously treated immune thrombocytopenia - a systematic review and network meta-analysis. Hematology. 2019; 24: 290-9.
11. Cuker A, Buckley B, Mousseau MC, Barve AA, Haenig J, Bussel JB. Early initiation of second-line therapy in primary immune thrombocytopenia: insights from real-world evidence. Ann Hematol. 2023; 102: 2051-8.
12. Mahévas M, Fain O, Ebbo M, Roudot-Thoraval F, Limal N, Khellaf M, et al. The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study. Br J Haematol. 2014; 165: 865-9.
13. Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. Haematologica. 2019; 104: 1112-23.
14. González-López TJ, Pascual C, Álvarez-Román MT, Fernández-Fuertes F, Sánchez-González B, Caparrós I, et al. Successful discontinuation of eltrombopag after complete remission in patients with primary immune thrombocytopenia. Am J Hematol. 2015; 90: E40-3.
15. Ghadaki B, Nazi I, Kelton JG, Arnold DM. Sustained remissions of immune thrombocytopenia associated with the use of thrombopoietin receptor agonists. Transfusion. 2013; 53: 2807-12.
16. Mishra K, Pramanik S, Jandial A, Sahu KK, Sandal R, Ahuja A, et al. Real-world experience of eltrombopag in immune thrombocytopenia. Am J Blood Res. 2020; 10: 240-51.

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# Blood Gas Measurements Using Point-of-Care Testing Devices in Pediatric Patients

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## ABSTRACT

**Introduction:** There is an increasing use of point-of-care testing (POCT) devices for patients. These portable devices are preferred by healthcare personnel because they are quick and easy to use. The aim of this study was to investigate whether POCT devices can provide rapid and reliable blood gas measurements.

**Methods:** Blood gas measurements were performed for 30 pediatric patients at the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital using a POCT device and a fully automatic blood gas analyzer. Eleven parameters (pH, $pCO_2$, $pO_2$, sodium, potassium , calcium , glucose, lactate, hematocrit, $cHCO_3$, and $cSO_2$) were compared. The statistical analyses were performed using the NCSS software. To determine the correlation between the two methods, the intraclass correlation coefficient (ICC) was calculated, and Bland-Altman graphs were used.

**Results:** The ICC demonstrated an almost strong correlation with pH (ICC=0.889), $pCO_2$ (ICC=0.968), $pO_2$ (ICC=0.981), sodium (ICC=0.799), potassium (ICC=0.968), calcium (ICC=0.909), glucose (ICC=0.967), $cHCO_3$ (ICC=0.919) and $cSO_2$ (ICC=0.988) and moderate correlation with lactate (ICC=0.626) and hematocrit (ICC=0.491). All p-values were all <0.001 for all analytes.

**Conclusion:** The POCT device was compared with a fully automatic blood gas analyzer. Unjustified postponement of analysis in patients with respiratory failure, shock, or electrolyte disorders can delay the application of appropriate treatment. Not only the benefits of an accurate POCT measurement but also the benefits of clinical practice and process changes should be taken into consideration.

**Keywords:** Point-of-care testing devices, POCT, blood gas

## Introduction

Respiratory disorders, dehydration, and electrolyte disorders are among the most common causes of admission to the pediatric emergency department (ED) for all ages (1). Blood gas analyzers are widely used in modern intensive care units (ICU) and EDs, providing a basic metabolic panel for managing clinical conditions such as respiratory, circulatory, and electrolyte disorders.

Arterial blood gas (ABG) analysis is the traditional method for evaluating the ventilation and acid-base status of patients. Venous blood gas (VBG) has recently been accepted as an alternative analytical method for some clinical conditions. VBG analysis and $SpO_2$ measurement provide accurate information about the acid-base, ventilation, and oxygenation status of patients with critical disease in the ED and ICU (2). The National Academy of Clinical Biochemistry Laboratory Laboratory Medical Practice Guidelines recommend that ABG results be taken into consideration to improve the outcomes of patients in the ED and ICU (3).

Point-of-care testing (POCT) devices for the analysis of patient samples, which can generally be performed at bedside or in another place outside the clinical laboratory by health professionals without any laboratory training (4). Using POCTs fulfills the need for rapid results and immediate decision to initiate therapy. Sample transfer time to the laboratory can be saved, and clinical decision-making can be performed rapidly (5). However, increased costs for the purchase and maintenance of analyzers, personnel training, laboratory information system, quality control, and external quality assessment procedures are important for ISO 15189:2022 accreditation (6). POCT has shorter turnaround times (TAT) for blood gas analysis results than the central laboratory; therefore, it is a clinically important advantage in decision-making.

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The current study aimed to investigate whether POCT devices can provide rapid and reliable blood gas measurements, which are of critical importance for intensive care patients.

## Methods

Approval for the study was granted by the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-02-16, date: 05.02.2024). This observational cohort study included 30 pediatric patients hospitalized. In total, 69 arterial blood samples were collected from the 30 patients in accordance with the Clinical and Laboratory Standards Institute (CLSI) C46-A2 guidelines (7) and antisepsis rules. The samples were withdrawn into a 2 mL volume PICO syringe (Radiometer Medical ApS) and anticoagulated with 80 IU of lyophilized electrolyte-balanced heparin.

The samples were analyzed in accordance with the CLSI EP9-A2 guidelines (8) using POCT (Epoc blood analysis - Epocal Inc., Canada) and a fully automatic blood gas device (Cobas b221, Roche, Germany) in the central laboratory.

### Statistical Analysis

Statistical analyses were performed using the NCSS software (Number Cruncher Statistical System, 2007, Kaysville, UT, USA). To determine the level of agreement between the two devices, the intraclass correlation coefficient (ICC) was calculated. The Wilcoxon test was used to determine differences between dependent samples. A value of $p<0.05$ was set as statistically significant.

## Results

The two devices were compared in terms of 11 parameters; pH, $pCO_2$, $pO_2$, sodium ($Na^+$), potassium ($K^+$), calcium ($Ca^{++}$), glucose, lactate, hematocrit, $cHCO_3$, and $cSO_2$. The results comparing the blood gas measurements performed using POCT and a fully automatic blood gas analyzer in the central laboratory are shown in Table 1.

The ICC demonstrated almost perfect agreement with pH [ICC (95% confidence interval (CI): 0.889 (0.827, 0.930), $p<0.001$], $pO_2$ [ICC (95% CI): 0.981 (0.937, 0.991), $p<0.001$], $pCO_2$ [ICC (95% CI): 0.968 (0.883, 0.987), $p<0.001$], sodium [ICC (95% CI): 0.799 (0.556, 0.897), $p<0.001$], potassium [ICC (95% CI): 0.968 (0.815, 0.988), $p<0.001$], calcium [ICC (95% CI): 0.909 (0.856, 0.943), $p<0.001$], glucose [ICC (95% CI): 0.967 (0.947, 0.979), $p<0.001$], $cHCO_3$ [ICC (95% CI): 0.919 (0.259, 0.976), $p<0.001$] and $cSO_2$ [ICC (95% CI): 0.988 (0.965, 0.994), $p<0.001$] and moderate agreement with lactate [ICC (95% CI): 0.626 (0.409, 0.767), $p<0.001$] and hematocrit [ICC (95% CI): 0.491 (0.291, 0.650), $p<0.001$].

In the current study, pH, $pO_2$, sodium, potassium, $cHCO_3$, and $cSO_2$ levels were slightly higher with POCT than with Cobas, and a statistically significant difference was present ($p<0.001$).

$PCO_2$ and lactate levels were also slightly lower with POCT than with Cobas, and a statistically significant difference was also present ($p<0.001$).

Calcium ($p=0.066$), glucose ($p=0.141$) and hematocrit ($p=0.226$) levels did not show statistically significant differences, whereas glucose and hematocrit levels were slightly lower but calcium levels were slightly higher with POCT than with Cobas.

## Discussion

Blood gas analysis plays an important role in the diagnosis, follow-up, and clinical evaluation of critical patients (9,10). A blood gas analysis device can analyze the pH, partial carbon dioxide pressure ($pCO_2$), and partial oxygen pressure ($pO_2$). Moreover, current blood gas analyzers are more sophisticated and, at the same time, electrolyte measurements [sodium ($Na^+$), potassium ($K^+$), ionized calcium ($iCa2^+$), chloride ($Cl^-$)], metabolites (glucose, lactate), hematocrit, and co-oxymetry (total hemoglobin, oxyhemoglobin, carboxyhemoglobin, methemoglobin, and deoxyhemoglobin) are performed.

In critical patients presenting to the ED and patients admitted to the ICU and receiving fluid treatment, all electrolytes are routinely measured with automatic analyzers in the central laboratories of hospitals, but this is time-consuming. The TAT in the emergency laboratory of tertiary-level hospitals is mean 15 minutes (11). This generally delays the decisions that need to be made rapidly regarding electrolyte values.

**Table 1. Comparison of blood gas measurements performed using POCT and a fully automated blood gas analyzer in the central laboratory**

| Parameter | Epoc (mean ± SD) | Roche (mean ± SD) | Difference (95% CI) | p | ICC (95% CI) | p | Reference range |
|---|---|---|---|---|---|---|---|
| PH | 7.45±0.07 | 7.42±0.07 | 0.030 (0.027, 0.034) | <0.001** | 0.889 (0.827, 0.930) | <0.001** | 7.35-7.45 |
| $PCO_2$ | 39.46±8.42 | 40.74±8.49 | -1.278 (-1.692, -0.864) | <0.001** | 0.968 (0.883, 0.987) | <0.001** | 35-45 mmHg |
| $PO_2$ | 85.89±54.70 | 79.95±51.68 | 5.941 (3.839, 8.042) | <0.001** | 0.981 (0.937, 0.991) | <0.001** | 75-100 mmHg |
| Sodium | 139.65±5.02 | 137.87±5.25 | 1.786 (1.099, 2.472) | <0.001** | 0.799 (0.556, 0.897) | <0.001** | 135-145 mmol/L |
| Potassium | 3.78±0.81 | 3.64±0.84 | 0.143 (0.105, 0.181) | <0.001** | 0.968 (0.815, 0.988) | <0.001** | 3.5-5.0 mmol/L |
| Calsium | 1.20±0.12 | 1.19±0.13 | 0.012 (-0.001, 0.025) | 0.066 | 0.909 (0.856, 0.943) | <0.001** | 2.1-2.6 mmol/L |
| Glucose | 134.83±56.59 | 137.38±55.41 | -2.558 (-5.988, 0.872) | 0.141 | 0.967 (0.947, 0.979) | <0.001** | 70-100 mg/dL |
| Lactate | 2.46±1.46 | 3.34±2.96 | -0.876 (-1.336, -0.416) | <0.001** | 0.626 (0.409, 0.767) | <0.001** | 0.5-2.2 mmol/L |
| Hematocrit | 33.68±6.04 | 34.55±5.70 | -0.871 (-2.292, 0.550) | 0.226 | 0.491 (0.291, 0.650) | <0.001** | 38-46% (female), 42-54% (male) |
| $cHCO_3$ | 27.21±4.81 | 25.63±4.70 | 1.579 (1.293, 1.866) | <0.001** | 0.919 (0.259, 0.976) | <0.001** | 22-28 mmol/L |
| $cSO_2$ | 82.83±21.68 | 80.96±23.06 | 1.871 (1.156, 2.584) | <0.001** | 0.988 (0.965, 0.994) | <0.001** | 95-100% |

**p<0.01, ICC: Intraclass correlation coefficient, CI: Confidence Interval, SD: Standard deviation, POCT: Point-of-care testing, POCT: Point-of-care testing

Blood gas analysis can be performed in central laboratories using conventional devices or in the wards, in inpatient services, operating rooms, and ICUs using a POCT device. These devices are used to support emergency interventions for patients (9,12). POCT provides clinical benefits by allowing clinicians to initiate appropriate treatment for emergency conditions. In central laboratories, where a small number of blood gas analyses are performed, calibrations performed several times a day increase costs. Therefore, POCT is economically more advantageous in these centers (13).

In patients followed-up in the ICU, the ventilation and oxygenation targets determine the treatment plan. Traditionally, arterial oxygen concentration (measured as partial oxygen pressure $PaO_2$) and pulse oximetry are used in the follow-up of oxygen saturation. The general recommendations for oxygenation are for the $PaO_2$ values to be 75-100 mmHg (14-16). The harmful effects of hypoxia are well known, and although most physicians tend to give more oxygen "just to be on the safe side" and to avoid hypoxia, hyperoxidation must also be avoided because oxygen can be toxic. Hypoxemia and hyperoxemia are harmful; therefore, oxygen therapy must be titrated (17).

In conditions such as hypoxemia, hypercarbia, and acidosis in ICU, the decision for starting treatment is critically important. Based on the current study findings, the use of a validated POCT device is recommended for the diagnosis and treatment of ABG abnormalities. In a study by Allardet-Servent et al. (18), the data from the central laboratory of 314 paired samples collected from 51 critical patients were reliably consistent with the POCT device results. In the present study, the correlation (ICC) between the two devices was determined to be 0.889 for the pH measurements, 0.981 for the $pO_2$ measurements, 0.968 for the $pCO_2$ measurements, and 0.988 for the $cSO_2$ measurements.

In critical patients, blood electrolytes are often measured, and the anion gap (AG) and strong ion difference (SID) are calculated from electrolyte measurements. These measurements play a role in guiding clinical decisions on improving acid-base status. In the present study, a strong correlation with sodium (ICC=0.799), potassium (ICC=0.968), and calcium (ICC=0.909) was observed.

The guidelines recommend that POCT can be used for ionized calcium analysis in ICU and potassium analysis in ED. However, during the preparation of the guidelines, there was insufficient evidence that POCT electrolyte results can improve clinical outcomes in an ICU setting (3). Several researchers have stated that caution should be exercised when interpreting electrolytes measured using various POCT devices. Correlation of the ionized calcium results for both devices in the guidelines were not observed in the current study. This may be due to the age distribution and pre-analytic problems.

In a study by Morimatsu et al. (19), the plasma sodium and chloride electrolyte concentrations were significantly different in the results obtained from two different measurement technologies, namely, POCT and laboratory devices. These differences in the measurements had a significant effect on the SID value (with similar large variations) calculated from the traditional AG value (large variations up to 15 mEq/L), and the individual electrolyte values (sodium and chloride). These large differences in electrolyte values and basic acid-base variables are clinically important and should be discussed in detail. Statistically significant differences were also found in the pH, potassium, and hematocrit measurements, which were due to differences in the calculated AG and SID (19,20). It has been reported in some studies that these differences are attributable to the automatic analyzers and chemical reactions used in the laboratory (21). It was shown in one study that the concentration of the measured electrolytes was reduced because taking the samples into tubes with heparin increased the volume and because of the binding of heparin to the electrolytes (22).

According to the US Clinical Laboratory Improvement Amendments 2006, deviations from the gold standard calibration measurements of 0.5 mmol/L in potassium and 4 mmol/L in sodium are accepted as normal (23).

There is currently strong evidence that indirect-ion selective electrode (ISE) sodium directly increases ISE measurements up to 4-10 mmol/L due to hypoproteinemia (24,25). Sodium and potassium measurements with direct ISE are recommended for critical patients. José and Preller (26) investigated the opinions of clinicians regarding the use of blood gas analyzers to measure potassium in acute conditions. The questionnaire results demonstrated that 52% of the clinicians preferred to wait for laboratory confirmation before making clinical decisions.

José and Preller (26) retrospectively compared 500 paired ABG samples performed within 1 h from central laboratory samples and found that 95% of the results had fallen to within 0.5 mmol/L difference limits. In a large retrospective study using a database including more than 11,000 matched samples performed within one hour, there was shown to be a strong correlation between the POCT and central laboratory results of sodium, potassium, and ionized calcium to enable clinicians to make clinical decisions immediately (27).

The advantage of POCT use rather than laboratory testing in the monitoring of blood glucose levels is that it allows insulin adjustments to be made more rapidly and more often. In the current study, a strong correlation with glucose (ICC=0.967) was found. The glucose results obtained from the device should be interpreted with caution. Inaccuracy of measurement should not be allowed despite the speed. In a study by Shearer et al. (28), POCT glucose values measured from central catheter or fingertip samples were significantly different from laboratory glucose values. There was observed to be a difference of at least 20 mg/dL between the POCT values and the laboratory glucose values in approximately 20% of the patients, which was clinically significant. Sensitivity of glucose measurement is extremely important. The accuracy of POCT is not sufficiently definitive for insulin management protocols with narrow glucose ranges. Most patient glucose measurement devices are designed to monitor glucose level curves, not based on single glucose values (28). In another study regarding personnel and POCT equipment costs, it was shown that the costs of POCT were higher than those of the laboratory analysis (29).

Normal acid-base homeostasis is a serious problem in ICU. In critical patients with acute kidney damage and lactic acidosis, acid-base disorders can be treated with continuous renal replacemant therapy (CRRT) (30). Urea, lactate, hydrogen ($H^+$), toxic substances, and drugs are eliminated from the blood following CRRT. In the decision to use CRRT,

pH, bicarbonate, and lactate levels are monitored during the follow-up of acidosis and the efficacy of CRRT. In the current study, a strong correlation with $HCO_3$ (ICC=0.919) and a moderate correlation with lactate (ICC=0.626) was found.

In conditions requiring emergency intervention, the turn-around time for blood gas analysis is extremely important in the management of critical patients.

In a randomized, controlled study to evaluate the efficacy of POCT in dehydration, anemia, and electrolyte abnormalities in pediatric ED, the time to POCT test results was 65 min, which reduced the decision time by 45 min, and consequently the time spent in ED was reduced by 39 min (31). Using the data from that study, Whitney et al. (32) calculated a cost saving of USD 303.30 per patient. According to another study conducted in pediatric ED, clinicians reported that as the availability of the tests increases, POCT is more advantageous, and its areas of use should be expanded (33).

POCT can provide results in a shorter TAT. There is evidence that, although not always, in many conditions, this provides an advantage in clinical decision-making compared with central laboratory services. A rapid TAT also provides the advantage of more effective time spent on admission or discharge of the patient. When POCT is considered to be generally more expensive than central laboratory testing, tests with higher clinical efficiency are important for preferring POCT (34).

## Conclusion

Based on the results of this study, POCT using a validated device can be recommended for the diagnosis and treatment of ABG abnormalities. Unjustified postponement of analysis in patients with respiratory failure, shock, or electrolyte disorders can delay the application of appropriate treatment. Accurate POCT measurements provide high quality data in clinical practice. The definition and application of evidence-based practice guidelines should be encouraged.

**Ethics Committee Approval:** Approval for the study was granted by the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2024-02-16, date: 05.02.2024).

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## References

1. Wier LM, Yu H, Owens PL, Washington R. Overview of children in the emergency department, 2010. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Agency for Healthcare Research and Quality (US), Rockville (MD); 2006.
2. Zeserson E, Goodgame B, Hess JD, Schultz K, Hoon C, Lamb K, et al. Correlation of Venous Blood Gas and Pulse Oximetry With Arterial Blood Gas in the Undifferentiated Critically Ill Patient. J Intensive Care Med. 2018; 33: 176-81.
3. Nichols JH, Christenson RH, Clarke W, Gronowski A, Hammett-Stabler CA, Jacobs E, et al. Executive summary. The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline: evidence-based practice for point-of-care testing. Clin Chim Acta. 2007; 379: 14-28.
4. Price CP. Evidence-based laboratory medicine: supporting decision-making. Clin Chem. 2000; 46: 1041-50.
5. Hawkins RC. Laboratory turnaround time. Clin Biochem Rev. 2007; 28: 179-94.
6. International Organization for Standardization. ISO 15189: 2022 Medical Laboratories Requirements for Quality and Competence. ISO; 2022.
7. D'Orazio P, Ehrmeyer SS, Jacobs E, Toffaletti JG, Wandrup JH. Blood gas and pH analysis and related measurements; approved guideline–. CLSI Document C46-A2. 2nd Ed. Wayne (PA:): Clinical and Laboratory Standards Institute, 2009.
8. Krouwer JS, Tholen DW, Garber CC, Goldschmidt HMJ, Kroll MH, Linnet K, et al. Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition. NCCLS and CLSI Document EP09-A2, 2002.
9. Benoit MO, Paul JL. Evaluation and advantages of an automatic magnetic mixing of syringes integrated to a whole blood gas analyser. Scand J Clin Lab Invest. 2009; 69: 628-32.
10. Scott MG, editors. Electrolytes and blood gases. Tietz Textbook of Clinical Chemistry, 1999. p. 431-440.
11. Cox CJ. Acute care testing. Blood gases and electrolytes at the point of care. Clin Lab Med. 2001; 21: 321-35.
12. Patel KP, Hay GW, Cheteri MK, Holt DW. Hemoglobin test result variability and cost analysis of eight different analyzers during open heart surgery. J Extra Corpor Technol. 2007; 39: 10-7.
13. Price CP. Medical and economic outcomes of point-of-care testing. Clin Chem Lab Med. 2002; 40: 246-51.
14. Fan E, Needham DM, Stewart TE. Ventilatory management of acute lung injury and acute respiratory distress syndrome. JAMA. 2005; 294: 2889-96.
15. Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000; 342: 1301-8.
16. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998; 338: 347-54.
17. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008; 12: R156.
18. Allardet-Servent J, Lebsir M, Dubroca C, Fabrigoule M, Jordana S, Signouret T, et al. Point-of-Care Versus Central Laboratory Measurements of Hemoglobin, Hematocrit, Glucose, Bicarbonate and Electrolytes: A Prospective Observational Study in Critically Ill Patients. PLoS One. 2017; 12: e0169593.
19. Morimatsu H, Rocktäschel J, Bellomo R, Uchino S, Goldsmith D, Gutteridge G. Comparison of point-of-care versus central laboratory measurement of electrolyte concentrations on calculations of the anion gap and the strong ion difference. Anesthesiology. 2003; 98: 1077-84.

20. Prichard JS, French JS, Alvar N. Clinical evaluation of the ABL-77 for point-of-care analysis in the cardiovascular operating room. J Extra Corpor Technol. 2006; 38: 128-33.

21. Jacobs E, Ancy JJ, Smith M. Multi-site performance evaluation of pH, blood gas, electrolyte, glucose, and lactate determinations with the GEM Premier 3000 critical care analyzer. Point of Care. 2002; 1: 135-44.

22. D'Orazio P, Miller WG, Myers GL, Doumas BT, Eckfeldt JH, Evans SA, et al. Standardization of Sodium and Potassium Ion-Selective Electrode Systems to the Flame Photometric Reference Method; Approved Standard—Second Edition. Clinical and Laboratory Standards Institute. 2000; 20: C29-A2.

23. Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments (CLIA). 2018 (cited 2023 May) Available from: URL: https://www.cdc.gov/clia/index.html#:~:text=The%20Clinical%20Laboratory%20Improvement%20Amendments,%2C%20prevent%2C%20or%20treat%20disease

24. Dimeski G, Morgan TJ, Presneill JJ, Venkatesh B. Disagreement between ion selective electrode direct and indirect sodium measurements: estimation of the problem in a tertiary referral hospital. J Crit Care. 2012; 27: 326.

25. Langelaan ML, Kamp L, Zandijk E, Raijmakers MT. Prevalence of pseudonatremia in a clinical laboratory - role of the water content. Clin Chem Lab Med. 2017; 55: 546-53.

26. José RJ, Preller J. Near-patient testing of potassium levels using arterial blood gas analysers: can we trust these results? Emerg Med J. 2008; 25: 510-3.

27. Mirzazadeh M, Morovat A, James T, Smith I, Kirby J, Shine B. Point-of-care testing of electrolytes and calcium using blood gas analysers: it is time we trusted the results. Emerg Med J. 2016; 33: 181-6.

28. Shearer A, Boehmer M, Closs M, Dela Rosa R, Hamilton J, Horton K, et al. Comparison of glucose point-of-care values with laboratory values in critically ill patients. Am J Crit Care. 2009; 18: 224-30.

29. Howanitz PJ, Jones BA; College of American Pathologists. Comparative analytical costs of central laboratory glucose and bedside glucose testing: a College of American Pathologists Q-Probes study. Arch Pathol Lab Med. 2004; 128: 739-45.

30. Cerdá J, Tolwani AJ, Warnock DG. Critical care nephrology: management of acid-base disorders with CRRT. Kidney Int. 2012; 82: 9-18.

31. Hsiao AL, Santucci KA, Dziura J, Baker MD. A randomized trial to assess the efficacy of point-of-care testing in decreasing length of stay in a pediatric emergency department. Pediatr Emerg Care. 2007; 23: 457-62.

32. Whitney RE, Santucci K, Hsiao A, Chen L. Cost-effectiveness of point-of-care testing for dehydration in the pediatric ED. Am J Emerg Med. 2016; 34: 1573-5.

33. Milner DHK. Is the point-of-care testing program meeting the pediatric emergency department's needs? Point of Care. 2014; 13: 31-4.

34. Lee-Lewandrowski E, Lewandrowski K. Perspectives on cost and outcomes for point-of-care testing. Clin Lab Med. 2009; 29: 479-89.

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# How Ready is Primary Care for Mpox (Monkeypox)? Mpox Knowledge Level Among Family Physicians: A Prospective Cross-sectional Study

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## ABSTRACT

**Introduction:** Mpox can cause serious complications and is a public health concern. Family physicians are the first healthcare professionals patients can apply for health. This study aimed to evaluate the level of knowledge of family physicians about mpox.

**Methods:** This prospective, descriptive, cross-sectional study was conducted. A survey was conducted between March 14, 2023 and April 14 of 2023 to evaluate the knowledge of mpox among 102 family physicians in Gaziantep, Turkey. The collected data were analyzed to determine physicians' knowledge of the disease, its symptoms, transmission, and treatment options.

**Results:** At the 80% cut-off, 8.8% of family physicians had good knowledge; at the 70% cut-off, 35.3% of physicians had good knowledge. The highest level of knowledge was observed in those working for 5 years or less; the lowest level was observed in those working for 6-15 years (p=0.045). The most correct answer (n=98) was "What is the type of microorganism that causes mpox?". The question with the most incorrect answers (n=90) was "A definitive diagnosis is made using ELISA tests".

**Conclusion:** Family physicians are the first health professionals to access the virus, particularly in cases of community transmission. Identify areas where physicians need additional education and training to better diagnose and treat mpox.

**Keywords:** Mpox, monkeypox, family physician, knowledge, primary care

## Introduction

The mpox virus was first described in 1958. It was found in Macaca fascicularis, an Asian monkey used for polio immunization research at a laboratory in Denmark. Human mpox, a disease transmitted by the mpox virus, is therefore a zoonotic infection (1-3).

The first reported case of human mpox was in the Democratic Republic of Congo in 1970. It is most common in West and Central Africa. Since 2016, cases have been reported in the Central African Republic, Sierra Leone, Nigeria, and Liberia. In 2017, the largest outbreak of mpox was recorded in Nigeria, with 68 confirmed cases. It is recognized as an increasing public health threat, particularly in areas of West Africa where there is evidence of increased attack rates (3,4).

Human mpox cases have also been reported in the Americas, Europe, and Asia. The mpox virus was transmitted to the United States from prairie dogs imported from Africa. In the UK and Israel, patients were travelers returning from Nigeria. The first case of mpox in Asia was reported in Singapore in 2019, when a Nigerian tourist was attending a conference. On June 30, 2022, Turkey reported the first confirmed case of Mpox virus detected by polymerase chain reaction (5-7).

Although smallpox was eradicated in 1980, mpox continues to occur in central and western African countries. Since May 2022, cases have also been reported in countries outside Africa with no previously documented mpox transmission (2,8).

Mpox has a high potential to be spread (9). Widespread transmission can lead to serious problems both in and outside the country (10). These can have social or economic consequences. Considering that the negative effects of the COVID-19 pandemic are still being overcome (11), the importance of this situation is clear. The increasing number of human cases of mpox highlights the value of prevention, timely recognition, and prompt intervention and treatment by healthcare workers. Unfortunately, a World Health Organization (WHO) report has shown that one of the barriers to preventing the disease is a lack of knowledge about mpox, especially by healthcare professionals (12).

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Although mpox has only been reported in Turkey in a few cases (13), healthcare workers should be informed and prepared for mpox cases. International tourism and trade in Turkey (14) may increase the vulnerability of populations to human mpox transmission. Family physicians are usually the first healthcare professionals patients consult for health (15). Therefore, in this study, we aimed to evaluate the level of knowledge of family physicians regarding mpox.

## Methods

### Study Design, Setting, and Survey

The study used a prospective, descriptive, cross-sectional design, which provided a brief insight into the physician knowledge levels. The collected data were analyzed to determine physicians' knowledge of the disease, its symptoms, transmission, and treatment options.

A survey was conducted between March 14, 2023, and April 14 of 2023 to evaluate the knowledge of mpox among family physicians in Gaziantep, Turkey. This self-administered questionnaire was designed for family physicians in Gaziantep. Personal (age, gender) and professional information (branch, duration of profession) questions were followed by mpox knowledge level questions (multiple choice, 37 questions). The knowledge questionnaire was designed in the Turkish language based on current facts from the centers for disease control and prevention and WHO (3,16).

Gaziantep University Faculty of Medicine Local ethics committee approval and provincial health directorate permission (approval number: 2022/254, date: 03.08.2022) were obtained.

The questionnaire took approximately 10 minutes to complete. Participants' names were not collected to ensure anonymity and confidentiality. At the end of the survey, raw data were extracted and analyzed using statistical software.

The inclusion criteria were those family physicians in Gaziantep province who voluntarily agreed to participate in the study and completed the questionnaire. The exclusion criterion was who left the survey incomplete.

### Statistical Analysis

The data were analyzed using SPSS 21.0 with a 95% confidence level. The level of knowledge was calculated, and the kurtosis and skewness coefficients were analyzed to determine the suitability of the level for normal distribution. The obtained kurtosis and skewness values were between +3 and 3, indicating that the data in the study were distributed normally (17-19). The highest and lowest scores for correct answers were calculated as percentages. Consequently, parametric test techniques were applied. The t-test and ANOVA were used to investigate differences in knowledge level based on demographic characteristics. The t-test was used to analyze demographic variables with 2 groups, while the ANOVA test was used to analyze variables in the k (k >2) groups. The association between categorical variables and willingness to receive training on Mpox disease was examined using the chi-squared test. Two cut-offs are used: 80% and a reduced cut-off of 70% to measure knowledge.

## Results

A total of 109 family physicians volunteered for the study. As 7 of them left the questionnaire incomplete, 102 were included in the analysis.

The mean and median knowledge scores were 0.53 and 0.57, respectively. The scores ranged from 0.05 to 0.92. When a cut-off of 80% was used, 9 out of 102 participants (8.8%) had good knowledge, whereas when the cutoff was reduced to 70%, 35.3% (36 out of 102) had good knowledge.

The age distribution of physicians was as follows: 31.4% were aged 30 years, 52% were between 31 and 40 years, and 16.7% were over 40. The mean age was 35.41±8.77 years. Approximately 53.9% were male and 46.1% were female. Approximately 76.5% of the patients were primary care practitioners and 23.5% were family medicine specialists.

40.2% of the physicians had been working for 5 years or less, 42.2% had been working for 6-15 years, and 17.6% had been working for more than 15 years. The mean professional experience of physicians was 9.98±9.14 years.

### Variables Related to Mpox Disease

Of these doctors, 95.1% (n=97) had heard of mpox. Only 2.9% (n=3) of the doctors were educated about mpox. Of the physicians surveyed, 87.9% (n=87) said they would like to be educated about mpox.

The values of the information level ranged from a minimum of 0.05 to a maximum of 0.92. The average value of the information level was 0.53, and the standard deviation was 0.18. The skewness value was 0.608. The kurtosis value was 0.070.

Questions with correct answers:

What type of microorganism causes Mpox? (n=98).

Initial symptoms include fever, severe headache, lymphadenopathy, back pain, myalgia, and severe fatigue (n=94).

Mpox can be transmitted from humans to humans (n=92).

Mpox does not infect children (n=85).

Antibiotics are effective against Mpox (n=84).

Questions with the most wrong answers:

A definitive diagnosis is made with ELISA tests (n=90).

It is not necessary for the sample to have a culture medium in the tube (n=89).

There is no vaccine available worldwide specifically for Mpox disease (n=86).

More rash is expected on the trunk (n=85).

Mpox disease can be transmitted from humans to humans through droplets (n=76) (Table 1).

There was a statistically significant difference in knowledge level based on years spent in the profession (p=0.045). The highest level of knowledge was observed in those working for 5 years or less, whereas the lowest level was observed in those working for 6-15 years. Age (p=0.138), gender (p=0.577), position, and willingness (p=0.736) to

receive training on the Mpox did not exhibit a statistically significant difference in knowledge level (Table 2).

There is no statistically significant correlation between the willingness to be educated about mpox and age (p=0.462), gender (p=0.200), position (p=0.621) or time in the profession (p=0.498).

## Discussion

In this study, we found that family physicians had a high level of awareness (96.1%) regarding the causative agent of Mpox. Knowledge of the causative agent is of great importance for appropriate disease management and treatment strategies (20-22).

**Table 1. Mpox knowledge levels**

| Question | Wrong answers, n (%) | Correct answers, n (%) | Mean ± SD of the correct answers |
|---|---|---|---|
| What type of microorganism causes Mpox? | 4 (3.9%) | 98 (96.1%) | 0.96±0.2 |
| Mpox can be transmitted from animals to humans. | 26 (25.5%) | 76 (74.5%) | 0.75±0.44 |
| Mpox can be transmitted from humans to humans. | 10 (9.8%) | 92 (90.2%) | 0.9±0.3 |
| Which of the following symptoms is associated with Mpox? | 33 (32.4%) | 69 (67.6%) | 0.68±0.47 |
| The initial symptoms include fever, severe headache, lymphadenopathy, back pain, myalgia, and intense fatigue. | 8 (7.8%) | 94 (92.2%) | 0.92±0.27 |
| The symptoms are similar to those of smallpox but are milder. | 50 (49%) | 52 (51%) | 0.51±0.5 |
| Mpox can be transmitted from humans to humans through droplets. | 76 (74.5%) | 26 (25.5%) | 0.25±0.44 |
| Mpox can be transmitted from humans to humans through sexual contact. | 59 (57.8%) | 43 (42.2%) | 0.42±0.5 |
| Mpox can be transmitted from humans to humans through blood transfusion. | 65 (63.7%) | 37 (36.3%) | 0.36±0.48 |
| Mpox can be transmitted from humans to humans through direct contact with non-intact skin (wound contamination). | 25 (24.5%) | 77 (75.5%) | 0.75±0.43 |
| Mpox can be transmitted from humans to humans through direct contact with intact skin. | 68 (66.7%) | 34 (33.3%) | 0.33±0.47 |
| Mpox can be transmitted through secretion by the infected person. | 34 (33.3%) | 68 (66.7%) | 0.67±0.47 |
| Transmission can occur by consuming the meat of infected animals (undercooked). | 67 (65.7%) | 35 (34.3%) | 0.34±0.48 |
| Consuming other animal products from infected animals is a possible risk factor. | 68 (66.7%) | 34 (33.3%) | 0.33±0.47 |
| Transmission of Mpox from animals to humans can occur through direct contact with infected animal blood, body fluids, or skin/mucous membrane lesions or through bites. | 28 (27.5%) | 74 (72.5%) | 0.73±0.45 |
| Rash does not occur on the face. | 56 (54.9%) | 46 (45.1%) | 0.45±0.5 |
| Rash can occur on the palms and soles. | 33 (32.4%) | 69 (67.6%) | 0.68±0.47 |
| Rash does not occur in the genitals. | 59 (57.8%) | 43 (42.2%) | 0.42±0.5 |
| More rash is expected on the trunk. | 85 (83.3%) | 17 (16.7%) | 0.17±0.37 |
| Mpox does not cause infection in children. | 17 (16.7%) | 85 (83.3%) | 0.83±0.37 |
| No vaccine is available worldwide specifically for Mpox disease. | 86 (84.3%) | 16 (15.7%) | 0.16±0.37 |
| Mpox is not lethal. | 42 (41.2%) | 60 (58.8%) | 0.59±0.49 |
| Antibiotics are effective against Mpox. | 18 (17.6%) | 84 (82.4%) | 0.82±0.38 |
| Antivirals are effective against Mpox. | 43 (42.2%) | 59 (57.8%) | 0.58±0.5 |
| Definitive diagnosis is made using PCR tests. | 23 (22.5%) | 79 (77.5%) | 0.77±0.42 |
| Mpox is less contagious and causes less severe disease than smallpox. | 43 (42.2%) | 59 (57.8%) | 0.58±0.5 |
| Vaccines against smallpox also protect against Mpox. | 65 (63.7%) | 37 (36.3%) | 0.36±0.48 |
| The natural hosts are rodents such as mice, rats, and squirrels. | 58 (56.9%) | 44 (43.1%) | 0.43±0.5 |
| The incubation period of Mpox from risky contact with the onset of symptoms, is usually 6-14 days. | 41 (40.2%) | 61 (59.8%) | 0.6±0.49 |
| The incubation period can be extended up to 21 days. | 45 (44.1%) | 57 (55.9%) | 0.56±0.5 |
| The rash usually starts within 1-3 days after the onset of fever. | 41 (40.2%) | 61 (59.8%) | 0.6±0.49 |
| Sequence of rash development. | 42 (41.2%) | 60 (58.8%) | 0.59 |
| The most suitable diagnostic samples for mpox are skin lesions. | 39 (38.2%) | 63 (61.8%) | 0.62±0.49 |
| The most suitable diagnostic samples for mpox are obtained from throat swabs. | 62 (60.8%) | 40 (39.2%) | 0.39±0.49 |
| The most appropriate diagnostic samples for mpox are blood cultures. | 71 (69.6%) | 31 (30.4%) | 0.3±0.46 |
| It is not necessary for the sample to have a culture medium in the tube. | 89 (87.3%) | 13 (12.7%) | 0.13±0.34 |
| Definitive diagnosis is made using ELISA. | 90 (88.2%) | 12 (11.8%) | 0.12±0.32 |

PCR: Polymerase chain reaction, SD: Standard deviation

**Table 2. Investigation of knowledge level in terms of variables**

| | | Knowledge level | T, F | p |
|---|---|---|---|---|
| | | Mean ± SD | | |
| Age[b] | 30 years and under | 0.58±0.17 | 2.023 | 0.138 |
| | 31-40 years | 0.51±0.18 | | |
| | Above 40 years | 0.49±0.2 | | |
| Gender[a] | Male | 0.52±0.19 | -0.560 | 0.577 |
| | Female | 0.54±0.18 | | |
| Position[a] | Family physician | 0.53±0.19 | -0.283 | 0.778 |
| | Family medicine specialist | 0.54±0.14 | | |
| Time in profession (years)[b] | 5 years and less | 0.58±0.17 | 3.195 | 0.045* |
| | 6-15 years | 0.48±0.19 | | |
| | Over 15 years | 0.53±0.16 | | |
| Would you like to be educated about Mpox?[a] | Yes | 0.53±0.17 | -0.339 | 0.736 |
| | No | 0.55±0.24 | | |

[a]: t test, [b]: ANOVA test, SD: Standard deviation

Alshahrani et al.'s (23) study in Saudi Arabia, which showed that the general level of knowledge about mpox among physicians was low, was similar to the results of the current study. These findings highlight the lack of knowledge about mpox among physicians and underscore the need for a better global understanding of the modes of transmission, diagnosis, and treatment of mpox.

Only 25% of the family physicians were aware of droplet transmission of mpox, indicating a significant training gap. Lack of knowledge may lead to inadequate isolation and infection control measures, which is of concern because of the potential for transmission by intradermal or respiratory routes (24-26).

The current study showed that most physicians accurately defined the incubation period of the mpox virus as ranging from 6 to 14 days, although fewer were aware that it could extend up to 21 days. This information is crucial for effective isolation protocols. In a study conducted by Gonzales-Zamora et al. (27) in Peru on the knowledge level of physicians regarding mpox, they were asked whether the incubation period was between 5 and 21 days, and most physicians provided the correct answer. The study conducted in Peru showed that although physicians had higher knowledge scores, they reported similar concerns regarding competence and preparedness. These findings indicate the need for more comprehensive education in this field.

The current study emphasizes that although palmar and plantar skin lesions are more commonly recognized, there is a lack of awareness regarding their symptomatology, particularly facial and genital lesions. In reviewing the literature, it was noted that other studies have asked questions about rash, but the difference in location of lesions was not questioned in detail (27-29).

This knowledge gap, which was also observed in a study conducted by Sahin et al. (29) for physicians in a university hospital in Turkey, points to the need for detailed training on the differential diagnosis of Mpox, not only in primary health care but also at all levels.

In the present study, only 2.9% of the physicians had received education on mpox. Other studies have also shown a small number of physicians educated on this subject, regardless of the results (19,23).

The study found that young physicians had a higher level of knowledge regarding mpox. This highlights the significance of ongoing education for medical professionals at all levels of experience. In addition, addressing challenges in effectively transferring knowledge is crucial. These challenges include the continuous growth of literature, the limited time, and difficulties in retaining information. Innovative methods, including the use of social media and multimedia tools, can play an important role in overcoming these barriers (30,31). The finding that recently graduated physicians had higher levels of knowledge about mpox may be a result of adapting their educational strategies to evolving communication methods, possibly due to their greater interaction with modern technological tools.

### Study Limitations

This study has limitations. A major earthquake in Turkey on February 6, 2023 (32) also affected the province of Gaziantep and limited access to family physicians. The authors were uncertain about the sincerity of the doctors' responses due to the use of multiple-choice questions. However, this negative potential was eliminated by directly communicating the survey questions to the family physicians and obtaining their consent.

## Conclusion

In conclusion, this study highlighted a moderate level of Mpox knowledge among family physicians, and similar findings from international studies underscore the need for a global educational intervention. These interventions should aim to update GPs' knowledge of mpox, focusing on areas such as transmission, symptomatology and diagnosis. To ensure effective management of emerging infectious diseases such as Mpox, comprehensive, continuous, and technologically adaptive educational efforts are essential.

**Ethics Committee Approval:** Gaziantep University Faculty of Medicine Local Ethics Committee approval and provincial health directorate permission (approval number: 2022/254, date: 03.08.2022) were obtained.

**Informed Consent:** It was obtained.

**Authorship Contributions:** Concept - Y.B.A., H.S.K., A.Ş.; Design - Y.B.A., H.S.K., A.Ş.; Data Collection or Processing - Y.B.A., H.S.K.; Analysis or Interpretation - Y.B.A., H.S.K., A.Ş.; Literature Search - Y.B.A., H.S.K., A.Ş.; Writing - Y.B.A., H.S.K., A.Ş.

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## References

1. Lee-Lewandrowski E, Lewandrowski K. Perspectives on cost and outcomes for point-of-care testing. Clin Lab Med. 2009; 29: 479-89.
2. Petersen E, Kantele A, Koopmans M, Asogun D, Yinka-Ogunleye A, Ihekweazu C, et al. Human Monkeypox: Epidemiologic and Clinical Characteristics, Diagnosis, and Prevention. Infect Dis Clin North Am. 2019; 33: 1027-43.
3. WHO. Mpox. World Health Organization; Accessed: 2024, Aug 1. Available from: https://www.who.int/news-room/fact-sheets/detail/monkeypox
4. Durski KN, McCollum AM, Nakazawa Y, Petersen BW, Reynolds MG, Briand S, et al. Emergence of Monkeypox - West and Central Africa, 1970-2017. MMWR Morb Mortal Wkly Rep. 2018; 67: 306-10.
5. Erez N, Achdout H, Milrot E, Schwartz Y, Wiener-Well Y, Paran N, et al. Diagnosis of Imported Monkeypox, Israel, 2018. Emerg Infect Dis. 2019; 25: 980-3.
6. Harapan H, Setiawan AM, Yufika A, Anwar S, Wahyuni S, Asrizal FW, et al. Knowledge of human monkeypox viral infection among general practitioners: a cross-sectional study in Indonesia. Pathog Glob Health. 2020; 114: 68-75.
7. Derin O, Öztürk EN, Demirbaş ND, Sevgi DY, Dökmetaş İ. Genital Erüpsiyonla Başvuran Bir Hasta: Türkiye'deki İkinci Maymun Çiçeği Olgusu [A Patient Presented with Genital Eruptions: The Second Case of Monkeypox from Türkiye]. Mikrobiyol Bul. 2023; 57: 134-40.
8. Ng YY, Azidah AK. Monkeypox: A review of data essential in primary care. Malays Fam Physician. 2023; 18: 9.
9. Kmiec D, Kirchhoff F. Monkeypox: A New Threat? Int J Mol Sci. 2022; 23: 7866.
10. Çelik M, Acar U, Akgul F, Arslan Y, Ceylan MR. Threat of mpox (monkeypox) outbreak after the COVID-19 pandemic: are healthcare professionals ready for new psychological wars? J Contemp Med. 2023; 13: 966-74.
11. Alshahrani AM. Cost-Benefit Analysis of Interventions to Mitigate the Monkeypox Virus. Int J Environ Res Public Health. 2022; 19: 13789.
12. World Health Organization. (2018). Monkeypox: current status in West and Central Africa: report of a WHO informal consultation, Geneva, Switzerland, 3 November 2017. World Health Organization. https://iris.who.int/handle/10665/272620.
13. WHO. Summary of number of probable and confirmed cases of mpox as well as deaths, by reporting country/area, European Region, TESSy, 2022-2023. Accesed: 2024, Aug 1. - https://cdn.who.int/media/docs/librariesprovider2/monkeypox/monkeypox_euro_ecdc_draft_jointreport_2023-01-04.pdf?sfvrsn=6a5e90bf_4&download=true
14. Alola UV, Cop S, Adewale Alola A. The spillover effects of tourism receipts, political risk, real exchange rate, and trade indicators in Turkey. Int J Tour Res. 2019; 21: 813-23.
15. Efeoğlu İE, Kılınçarslan Ö. Pandemic experiences of family physicians infected with the COVID-19: a qualitative study. BMJ open. 2022; 12: e052955.
16. CDC. Mpox. Clinical Guidance Accessed: 2024, Aug 1. - https://www.cdc.gov/poxvirus/mpox/clinicians/clinical-guidance.html
17. Groeneveld RA, Meeden G. Measuring Skewness and Kurtosis. The Statistician. 1984; 33: 391-9.
18. Hopkins KD, Weeks DL. Tests for Normality and Measures of Skewness and Kurtosis: Their Place in Research Reporting. Educ Psychol Meas Edu. 1990; 50: 717-29.
19. De Carlo LT. On the Meaning and Use of Kurtosis. Psychol Methods. 1997; 2: 292-307.
20. Rallapalli S, Razai MS, Majeed A, Drysdale SB. Diagnosis and management of mpox in primary care. JRSM. 2022; 115: 384-9.
21. CDC. Mpox Clinical Treatment. Accessed: 2024, Aug 1. https://www.cdc.gov/poxvirus/mpox/clinicians/treatment.html
22. Patel A, Bilinska J, Tam JCH, Da Silva Fontoura D, Mason CY, Daunt A, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. BMJ. 2022; 378: e072410.
23. Alshahrani NZ, Algethami MR, Alarifi AM, Alzahrani F, Alshehri EA, Alshehri AM, et al. Knowledge and Attitude Regarding Monkeypox Virus among Physicians in Saudi Arabia: A Cross-Sectional Study. Vaccines (Basel). 2022; 10: 2099.
24. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022; 22: 1153-62.
25. Kaya E, Şahin M, Solak Y, Acar O, Kuş C, Kuş MM, et al. An overview of mpox outbreak. Cent Asian J Med Hypotheses Ethics. 2023; 4: 13-21.
26. Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. N Engl J Med. 2022; 387: 679-91.
27. Gonzales-Zamora JA, Soriano-Moreno DR, Soriano-Moreno AN, Ponce-Rosas L, Sangster-Carrasco L, De-Los-Rios-Pinto A, et al. Level of Knowledge Regarding Mpox among Peruvian Physicians during the 2022 Outbreak: A Cross-Sectional Study. Vaccines (Basel). 2023; 11: 167.
28. Alkalash SH, Marzouk MM, Farag NA, Elesrigy FA, Barakat AM, Ahmed FA, et al. Evaluation of human monkeypox knowledge and beliefs regarding emerging viral infections among healthcare workers. Int J Emerg Med. 2023; 16: 75.
29. Sahin TK, Erul E, Aksun MS, Sonmezer MC, Unal S, Akova M. Knowledge and Attitudes of Turkish Physicians towards Human Monkeypox Disease and Related Vaccination: A Cross-Sectional Study. Vaccines (Basel). 2022; 11: 19.
30. Martin LJ, Turnquist A, Groot B, Huang SYM, Kok E, Thoma B, vanMerriënboer JJG. Exploringthe role of infographics for summarizing medical literature. Health Prof Educ. 2019; 5: 48-57.
30. Irfan KS, Farhana I, Eiad AF, Nassr AM, Al Mohammed AQ, Maya N, et al. Family physicians' utility of socialmedia: a survey comparison among family medicine residents and physicians. Afr J Health Sci. 2018; 18: 817-27.
31. Gök M, Melik MA, Doğan B, Durukan P. Hospital crisis management after a disaster: from the epicenter of 2023 Türkiye-Syria earthquake. TJTES. 2023; 29: 792-7.

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# Investigating Factors Influencing the Risk of Recurrence of Simple Bone Cysts: Retrospective Analyses of 41 Cases

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## ABSTRACT

**Introduction:** Recurrence is a major challenge in the treatment of solitary bone cysts (SBC). In this study, we aimed to analyze the factors that influence the risk of recurrence in patients with simple bone cysts.

**Methods:** The study included patients who underwent curettage and bone grafting for SBC between 2010 and 2021 at a single center. Data collected included age, sex, side, bone location, pathological fracture history, cyst activity, internal fixation, graft type, radiological features of the cyst (cyst index, cyst diameter ratio, cyst area and cyst length), follow-up time, and presence of recurrence. The Cox algorithm was applied to identify factors independently associated with SBC recurrence.

**Results:** A total of 41 patients with a mean age of 10.8±3.19 years (range 4-15 years) were included in this study. The average follow-up period was 51±21.3 months. Recurrence was observed in 13 of 41 patients during follow-up. There were no significant differences in sex, bone location, pathological fracture history, and the type of graft used between patients with and without recurrence. The age at surgery was found to be significantly lower in the recurrence group (p=0.02). The radiological features of the cyst: cyst index, cyst diameter ratio, cyst area, and cyst length, were found to be higher in the recurrence group, although there was no significant difference.

**Conclusion:** It is important to inform families that the risk of recurrence is high at a young age and in patients with large solitary bone cysts.

**Keywords:** Bone cyst, diameter, recurrence, radiological features

## Introduction

Solitary bone cysts (SBC) (also known as basic bone cysts, SBC) are benign non-tumoral lesions that usually present in the metaphyseal region of long bones in children and adolescents. This tumor-like lesion of unknown origin accounts for 3% of bone tumors, with 70% of them occurring in the proximal humerus and femur (1). The exact cause and pathogenesis of SBC remain unknown; venous obstruction, synovial tissue in the metaphysis, and delayed metaphyseal ossification have been hypothesized (2,3). The diagnostic radiological characteristic is a radiolucent, well-defined, geographic osteolytic lesion with a thin sclerotic margin that causes bone expansion and cortical thinning, seen on a direct X-ray. In magnetic resonance imaging (MRI), which is requested for differential diagnosis, a homogenous fluid-equivalent signal intensity is generally observed, although it varies depending on the amount of blood present (4).

Although they are usually asymptomatic, they can lead to pathological fractures and impairment of the normal growth and development of affected bones. There is no consensus on the best treatment option. There are many different treatment alternatives, including observation, minimally invasive surgery (percutaneous or endoscopic curettage, aspiration and steroid injection), and open curettage and grafting (5). Recurrence is a major issue in these alternative treatment approaches. Previous studies have reported active SBC and younger age as risk factors (6-8). In this study, we investigated and analyzed factors influencing the risk of recurrence in patients with simple bone cysts.

## Methods

IRB and İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee approval was obtained before the study initiation (approval number: 2024/611, date: 13.03.2024). The study included patients who underwent curettage and bone grafting (including the patients who received nail or plate fixation according to the fracture risk) for SBC between 2010 and 2021 at a single center. The inclusion criteria were a diagnosis of humerus and femur SBC, open physis at the operating bone, and a minimum follow-up of 2 years after surgery. The exclusion criteria were recurrent cases, pathologically unverified, and incomplete imaging

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(MRI, X-Ray) SBC patients (Figure 1). The informed consent of the parents and the consent of the child to participate was obtained.

**Patients' management and operation procedure:** In patients admitted to our outpatient clinic with a complaint of a pain at shoulder and hip joint, physical examination and radiological examinations were performed thoroughly. We generally perform magnetic resonance imaging evaluations in the differential diagnosis of aneurysmal bone cysts in aggressive lesions. Patients with pathological fractures of the proximal humerus were followed conservatively because they had the possibility of spontaneous healing. Lower extremity surgery was preferred. Intralesional resection based on the Musculoskeletal Tumor Society as defined by Enneking et al. (9) was used for SBC treatment.

After this, the surgeon decided to perform extended curettage and bone grafting with an allograft or bioactive glass graft (Bone-G, Meta Bioengineering). All surgeries were performed under general anesthesia by two surgeons (A.S. and S.B.) with expertise in orthopedic oncology while preparing the patients and placing them in the supine position and beach chair position. After administration (50 mg/kg, max, 1.5 gr) cefuroxime for prophylaxis, a deltopectoral incision was used for the humeral lesion and a modified anterolateral longitudinal incision (Watson Jones) for the femoral lesion. The bone window was opened using a burr or blade. After extended curettage, the medullary cavity was reammed to open vascular channels between the cysts and the intramedullary venous system. Pulsatile lavage was performed on the exposed bone using an isotonic solution, and the allograft or glass graft was impacted into the curing area of the bone. Plate fixation was performed in patients at risk of fracture (Figure 2).

**Postoperative management:** Postoperative pain management was provided with non-steroidal anti-inflammatory, tramadol, and

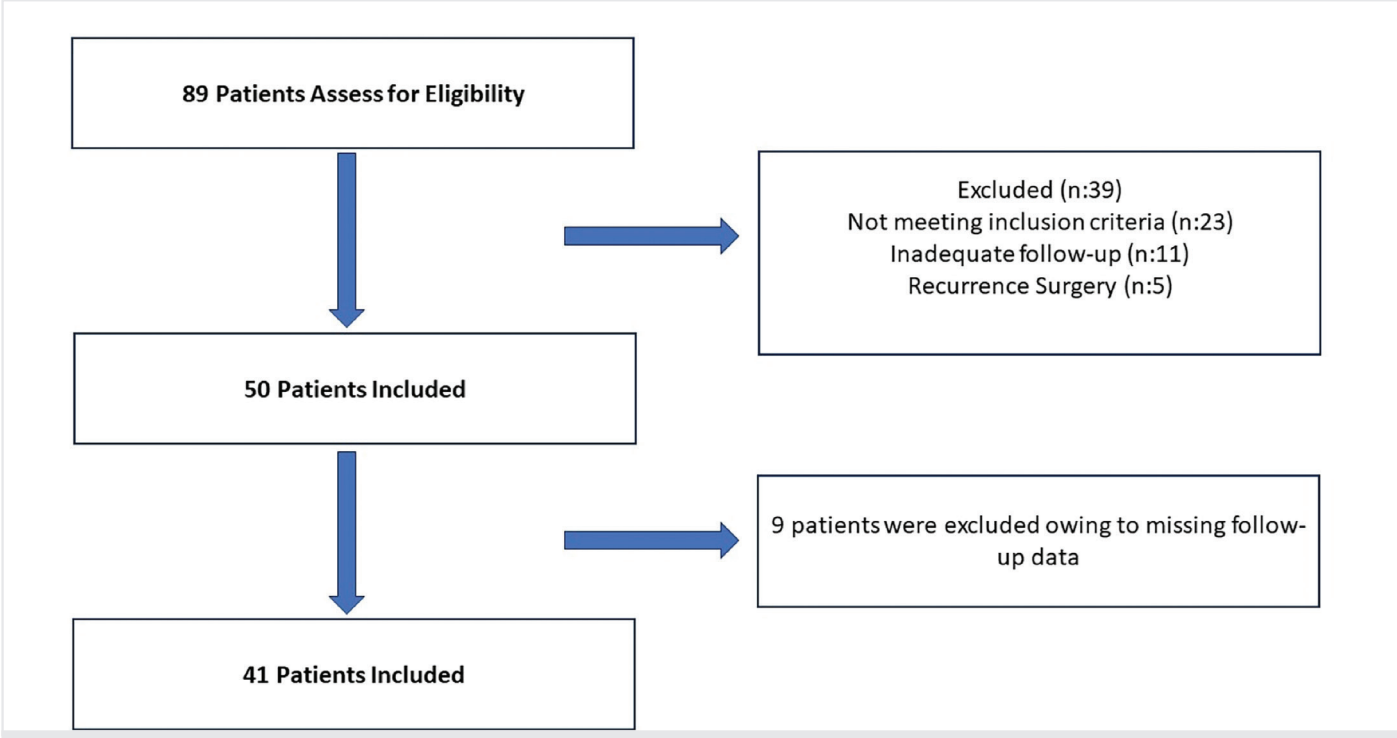


**Figure 1.** Flow chart

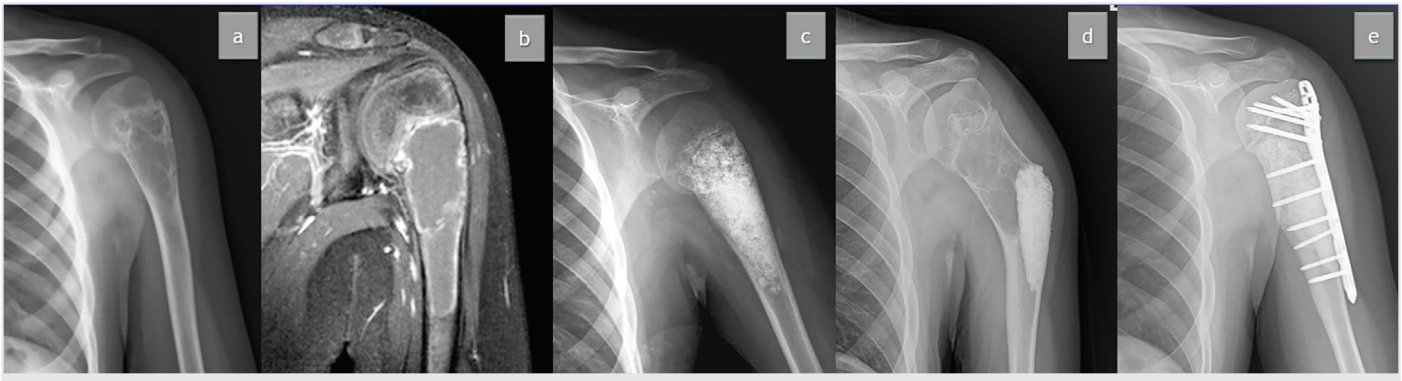


**Figure 2.** (a, b) A 10-year-old male patient was diagnosed with humerus SBC. (c) The patient was treated with curettage and grafting with bone glass graft (d) Recurrence and deformity are observed in the third postoperative year. (e) Follow-up radiograph of the patient after re-operation.
SBC: Solitary bone cysts

paracetamol as standard. Patients who underwent surgery for humeral SBC were followed up with arm sling for 2 weeks. First, active and passive ROM exercises were performed during follow-up. After the sixth week, no restrictions were applied. Femur SBC patients were mobilized with double crutches with non-weight bearing for six weeks. Active ROM exercises were performed starting from the postoperative period. After the sixth week, crutches were discontinued, and gradual loading was allowed. After the 12th week of surgery, patients were allowed to return to activities and sports.

**Radiological evaluation:** Standard anterior-posterior and lateral femur and anterior-posterior, oblique, and axillary humerus radiographs were obtained at the sixth week, third month, sixth month, and final visit. A Picture Archiving and Communication System (PACS) was used for radiological evaluation at our center. We used a Neers Modified Basic Bone Cyst classification system to standardize recurrence evaluation (10). Grades III and IV were considered as recurrence:

**Grade I-Healed:** Cyst formed with new bone, with or without a small radiolucent area(s) <1 cm in size.

**Grade II-Healed with defects:** Radiolucent area on X-ray <50% of the bone diameter with cortical thickness that does not pose a fracture risk.

**Grade III persistent cyst:** Radiolucent area >50% bone diameter, thin cortical margin; no enlargement of cyst size.

**Grade IV recurrent cyst:** Recurrence of a cyst in a previously excised area or an increase in the size of a radiolucent cyst.

SBCs were classified as active when they were less than 0.5 cm from the physis and as latent when they were not (10). The cyst mean area was calculated using the following formula: 0.5×D×d2. This was calculated considering that the SBC is ellipsoid and regular in form. The cyst index was calculated by dividing the cyst area by the cortical diameter, as described by Kaelin and MacEwen (11). The cyst diameter ratio was calculated by dividing the cyst longitudinal length by the bone diameter (12). All radiologic measurements were performed by a single experienced orthopedic surgeon using the hospital's (PACS™, Centricity Universal Viewer, GE Healthcare, Milwaukee). The magnification error was corrected by placing a metal ruler on the X-rays.

### Statistical Analysis

SPSS 26 software was used for statistical analyses. Descriptive statistical methods (mean, standard deviation, percentage) were used to evaluate the study data. The conformity of quantitative data to normal distribution was tested using Shapiro-Wilk test and graphical analyses. The significance of quantitative variables with normal distribution between the two groups was compared using Student's t-test. Mann-Whitney U test was used for comparisons of quantitative variables that did not show normal distribution between the two groups. Pearson's chi-square test and Fisher's exact test were used to compare qualitative data. Statistical significance was set as $p<0.05$. Recurrence factors were identified in the univariate analysis. Elements with p-values (two-sided) of 0.05 or less were included in the multivariate Cox model to identify independent variables in a stepwise manner.

## Results

A total of 41 patients were included in the study. In correlation with the male predominance of SBC, 36 patients (87%) were male. The mean patient age at operation was 10.8±3.19 years (range, 4-15 years). Twenty-five patients presented with SBC in the humerus and 16 in the femur. SBC was latent in 53% of patients. More than half of the patients had a history of pathological fracture.

The mean SBC area was 8.25±4.62 $cm^2$ (range, 1.1-26.2 $cm^2$). The mean SBC longitudinal length was 6.67±3.83 cm (range, 2.1-24.4 cm). The average SBC index was 4.58±2.61 ratio (range, 0.9-13.5). The mean SBC diameter ratio was 4.97±2.66 ratio (range, 1.85-12.96). The average follow-up period was 51±21.3 months (range, 25-112 months). Allografts were used in 27 patients and synthetic glass grafts in 14 patients. In four femur and two humerus SBC patients, plate fixation was used because of the risk of fracture. The demographic data of patients were also showed in Table 1.

Recurrence was observed in 13 of 41 patients during follow-up. The recurrence rate was 31%. Eight of these patients underwent re-operation, three underwent observation, and three were lost to follow-up. Deformity after recurrence was observed in only one patient in the study groups. This patient recovered after recurettage + grafting and plate fixation (Figure 2). There were no significant differences in sex, bone location, pathological fracture history, and the type of graft used between patients with and without recurrence. The age at surgery was found to be significantly lower in patients with recurrence (recurrence patients: 8.75±2.96 years, no recurrence: 11.07±2.82 years, p=0.02). The radiological features of the cyst: cyst index, cyst diameter ratio, cyst area, and cyst length, were found to be higher in the recurrence group, although there was no significant difference. The data comparing the radiological features of both groups are shown in Table 2.

**Table 1. Demographic and baseline data**

| | | Group | | Test value |
|---|---|---|---|---|
| | | Recurrence group, (n=13) | No recurrence group, (n=28) | p |
| Age | Mean ± SD | 8.75±2.96 | 11.07±2.82 | [a]**0.002*** |
| Sex | Male | 13 (100) | 23 (82) | [b]**0.104** |
| | Female | 0 | 5 (18) | |
| Bone | Humerus | 8 (61) | 17 (60) | [b]**0.960** |
| | Femur | 5 (39) | 11 (40) | |
| Localization | Metaphysis | 12 (92) | 23 (85) | [b]**0.641** |
| | Diaphysis | 1 (8) | 4 (15) | |
| Fracture history | Yes | 7 (53) | 16 (57) | [b]**0.843** |
| | No | 6 (47) | 12 (43) | |
| Follow-up time (month) | Mean ± SD | 43.83±14.16 | 54.73±22.82 | [a]**0.120** |

[a]Data analyses were performed with Independent samples t-test,
[b]Data analyses were performed using Pearson's chi-square test, *p<0.05,
SD: Standard deviation

**Table 2. Radiological findings of SBC and surgery type**

| | | Group | | Test value |
|---|---|---|---|---|
| | | Group 1 (n=13) | Group 2 (n=21) | p |
| Graft type | Allograft | 10 (76) | 17 (60) | **0.308**[a] |
| | Bone-glass | 3 (24) | 11 (40) | |
| Internal fixation | Yes | 1 (8) | 5 (18) | **0.391**[a] |
| | No | 12 (92) | 23 (82) | |
| Cyst activity | Active | 8 (61) | 11 (39) | **0.184**[a] |
| | Latent | 5 (39) | 17 (61) | |
| Cyst volume ($cm^2$) | Mean ± SD | 9,288±5,821 | 7,768±3,982 | **0.750**[b] |
| Cyst longtidunal size (cm) | Mean ± SD | 7.43±0.89 | 6.32±0.46 | **0.814**[b] |
| Cyst index | Mean ± SD | 5.69±3.24 | 4.07±2.14 | **0.121**[b] |
| Cyst diameter ratio | Mean ± SD | 5.63±3.54 | 4.65±2.14 | **0.515**[b] |

[a]Data analyses were performed using Fisher's exact test. [b]Data analyses were performed using the Mann-Whitney U test, *p<0.05, SD: Standard deviation, SBC: Solitary bone cysts

## Discussion

Younger age was the only significant factor associated with increased risk of recurrence. No significant relationship was found between the other factors determining the risk of recurrence. In another study assessing the predictive factors for recurrence of proximal humerus SBC, Teoh et al. (13) defined refracture and re-expansion of the cyst as recurrence. In this study, 31 of 32 patients presented with pathological fracture, and curettage was performed in only nine patients. Active cysts were not significantly associated with recurrence. They stated that a high cyst index, young age, and non-impacted pathological fracture significantly increased the risk of recurrence. It was mentioned that decreasing the cyst volume due to impaction may have a favorable effect on healing. In the present series, younger age at surgery was clinically significant in the recurrence group (p=0.02). Although mean SBC size, area, index, and diameter ratio were higher in the recurrence group, no clinically significant difference was detected.

In a systematic review of different treatment modalities for SBC, the healing rates of 3,217 patients were evaluated (8). Approximately 85% of these cases involved humerus and femur SBC. The M:F ratio was set to 2. Among the treatment modalities, the lowest healing rate was observed in observation (healing rate 64%), whereas the highest healing rates were observed in long bone SBC with open curettage and grafting (healing rate 90%) and elastic nailing without curettage (healing rate 100%). In this study, it was emphasized that the recovery rates of the most unsuccessful surgical treatments were higher than the observed rates. In addition, the success of allograft, autograft, and synthetic grafts as graft types was evaluated in cases with surgical curettage, and similar healing rates were observed. The higher recurrence rate (30%) in our series may be due to the longer follow-up period and smaller sample size. In addition, allograft and bioactive synthetic bone grafts were used. Because synthetic grafts are cheaper and more accessible, large-volume SBCs were used more frequently. Although there was a bias in the study, the graft types used did not have a clinically significant effect in recurrence (p=0.308).

There are several conflicting studies in the literature on the effects of pathological fracture development on the risk of recurrence. Flont et al. (6) retrospectively investigated the risk factors for recurrence in 24 patients with SBC. It was determined that patients with humeral SBC who had pathological fractures upon diagnosis were more likely to have recurrence. Radiological parameters such as cyst area, cyst index, and cyst diameter ratio were significantly lower in patients without recurrence. No significant difference was found in terms of age, gender, or type of bone graft. Researchers explained the negative effect of presentation with pathological fracture on prognosis as difficulty in surgical technique due to the irregularity in the cystic cavity after fracture. Nearly half of the patients in our study group had a history of pathological fracture. The pathological fracture history had no significant effect on recurrence. In contrast to this study, another retrospective study was conducted by Cha et al. (7) to determine the effect of pathological fracture on recurrence. A total of 54 patients (25 patients admitted pathological fractures) who underwent only retrograde elastic nailing (no curettage and grafting) due to femoral SBC were included in the study. The researcher found no significant difference in the average healing time between the two groups. The healing and recurrence rates were similar, suggesting that the presence of a pathologic fracture did not affect the outcome of intramedullary nailing treatment. Although pathological fracture history was present in nearly half of the patients in the present study group, it had no significant effect on recurrence (p=0.843).

### Study Limitations

Regarding methodology, the study's primary limitation is the small sample size. Another limitation is the retrospective nature of the study. The SBC series usually has a medium sample size, similar to our study. The results obtained during the mid-term follow-up will contribute to the literature. An important limitation of this study is that the treatment methods were not randomized.

## Conclusion

Since recurrence is one of the most challenging issues in the treatment of SBC and is frequently observed, this should be shared with the family, and it should be explained in detail that repeat surgical interventions may be required. It is important to inform the family that the risk of recurrence will be high at a young age and when the SBC is large. The treatment of SBC should be patient-specific. In patients with asymptomatic SBC detected at an early age, observation in the primary treatment plan instead of surgical treatment at a young age is more appropriate.

**Ethics Committee Approval:** IRB and İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee approval was obtained before the study initiation (approval number: 2024/611, date: 13.03.2024).

**Informed Consent:** The informed consent of the parents and the consent of the child to participate was obtained.

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

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## References

1. Wilkins RM. Unicameral bone cysts. J Am Acad Orthop Surg. 2000; 8: 217-24.
2. Mascard E, Gomez-Brouchet A, Lambot K. Bone cysts: Unicameral and aneurysmal bone cyst. Orthop Traumatol Surg Res. 2015; 101(Suppl 1): S119-27.
3. Jaffe HL, Lichtenstein L. Solitary Unicameralbone Bone Cyst with Emphasis on the Roentgen Picture, the Pathologic Appearance and the Pathogenesis. Arch Surg. 1942; 44: 1004-25.
4. Kang HS, Ahn JM, Kang Y. Oncologic Imaging: Bone Tumors. Springer; 2017.
5. Baghdadi S, Arkader A. Unicameral Bone Cysts: Treatment Rationale and Approach. J Pediatr Orthop Soc North Am. 2021; 3: 267.
6. Flont P, Malecki K, Niewola A, Lipczyk Z, Niedzielski K. Predictive characteristic of simple bone cyst treated with curettage and bone grafting. BMC Musculoskelet Disord. 2015; 16: 350.
7. Cha SM, Shin HD, Kim KC, Park JW. Does fracture affect the healing time or frequency of recurrence in a simple bone cyst of the proximal femur? Clin Orthop Relat Res. 2014; 472: 3166-76.
8. Kadhim M, Thacker M, Kadhim A, Holmes L Jr. Treatment of unicameral bone cyst: systematic review and meta analysis. J Child Orthop. 2014; 8: 171-91.
9. Enneking W, Dunham W, Gebhardt M, Malawar M, Pritchard D. A system for the classification of skeletal resections. Chir Organi Mov. 1990; 75(1 Suppl): 217-40.
10. Neer CS 2nd, Francis KC, Marcove RC, Terz J, Carbonara PN. Treatment of unicameral bone cyst. A follow-up study of one hundred seventy-five cases. J Bone Joint Surg Am. 1966; 48: 731-45.
11. Kaelin AJ, MacEwen GD. Unicameral bone cysts. Natural history and the risk of fracture. Int Orthop. 1989; 13: 275-82.
12. Kanellopoulos AD, Mavrogenis AF, Papagelopoulos PJ, Soucacos PN. Elastic intramedullary nailing and DBM-bone marrow injection for the treatment of simple bone cysts. World J Surg Oncol. 2007; 5: 111.
13. Teoh KH, Watts AC, Chee YH, Reid R, Porter DE. Predictive factors for recurrence of simple bone cyst of the proximal humerus. J Orthop Surg (Hong Kong). 2010; 18: 215-9.