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Comparative diagnostic value of novel and traditional anthropometric indices in FibroScan-diagnosed NAFLD among Turkish adults

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ABSTRACT

Aims: Nonalcoholic fatty liver disease (NAFLD) is a growing global health concern associated with chronic liver damage and metabolic comorbidities. Traditional anthropometric measures—such as body-mass index (BMI) and waist circumference (WC), have known limitations. This study aimed to compare the diagnostic performance of novel obesity indices, including a body shape index (ABSI) and body roundness index (BRI), with conventional parameters in predicting NAFLD.

Methods: A retrospective study was conducted with 430 Turkish adults (aged 18–74) undergoing FibroScan assessments. Anthropometric data (body weight, height, WC) and controlled attenuation parameter (CAP) values were collected. NAFLD was defined as CAP ≥257 dB/m. Predictive capabilities of BMI, WC, ABSI, BRI, waist-to-height ratio (WHtR), and body weight were compared using receiver operating characteristic (ROC) curve analyses. Pairwise area under-the-curve (AUC) comparisons were performed using the DeLong test, with significance set at $p<0.05$.

Results: Body weight displayed the highest area under the ROC curve (AUC) for NAFLD diagnosis (AUC=0.766; 95% CI: 0.716–0.816). BMI (AUC=0.695; 95% CI: 0.637–0.753) and WC (AUC=0.693; 95% CI: 0.636–0.750) had comparable performance. BRI and WHtR demonstrated lower AUC values (AUC=0.621), while ABSI had insufficient discriminatory ability (AUC=0.485). NAFLD prevalence was significantly higher in males (71% vs. 50%, $p<0.001$), aligning with prior epidemiological reports.

Conclusion: Among Turkish patients diagnosed via FibroScan, body weight emerged as the strongest predictor of NAFLD, with BMI and WC remaining reliable alternatives. Novel indices such as BRI and ABSI showed limited utility for clinical diagnosis. These findings highlight the continued relevance of simple and traditional measurements for identifying NAFLD risk.

Keywords: Nonalcoholic fatty liver disease (NAFLD), anthropometric indices, a body shape index (ABSI), body roundness index (BRI), FibroScan

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder worldwide, defined by the accumulation of fat in more than 5% of hepatocytes without secondary causes such as excessive alcohol consumption, viral and autoimmune hepatitis, or congenital liver diseases.[1-3] While most NAFLD patients exhibit isolated hepatic steatosis, a subset may progress to nonalcoholic steatohepatitis (NASH), which can lead to hepatic fibrosis and potentially cirrhosis, hepatocellular carcinoma, and end-stage liver disease.[4,5]

Obesity is a well-established risk factor for NAFLD.[6] Studies show that 50% of individuals with NAFLD and 82% of those with NASH are obese.[7] Given the growing burden of obesity-related diseases, anthropometric measures such as body-mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR) have been widely used to assess fatty liver disease severity.[8] BMI and WC are standard indices for evaluating overall and central obesity, known risk factors for NAFLD.[9-11] However, BMI does not differentiate between adipose and lean mass, and WC cannot distinguish visceral from subcutaneous fat distribution.[12-14]

To address these limitations, novel anthropometric indices have been developed, including a body shape index (ABSI) and body roundness index (BRI), which integrate BMI, WC, and height. These indices have been explored for their predictive value in metabolic disorders such as cardiovascular disease, diabetes mellitus, and NAFLD.[15-19]

FibroScan, a widely used noninvasive diagnostic tool, provides reliable quantification of hepatic steatosis and fibrosis using the controlled attenuation parameter (CAP). It offers a better correlation with hepatic fat content compared to conventional ultrasonography.[19-22]

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This study aims to determine the diagnostic value of traditional anthropometric measurements—BMI, WC, and WHtR—alongside the novel obesity indices ABSI and BRI in identifying NAFLD cases diagnosed via FibroScan. Additionally, we seek to establish which indices are the most robust predictors of NAFLD.

METHODS

Ethics

University of Health Sciences, Bursa Faculty of Medicine, Bursa City Training and Research Hospital Ethics Committee Institutional Review Board (IRB) approved the study protocol (Date: 22.01.2025, Decision No: 2025-2/15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

This retrospective study aimed to compare the predictive power of classic anthropometric measurements—BMI and WC with the novel obesity indices ABSI and BRI for diagnosing NAFLD in adult patients who received a NAFLD diagnosis via FibroScan. Additionally, it sought to determine which index might be more clinically relevant in routine practice.

The study encompassed patients who presented to the gastroenterology outpatient clinic between September 1, 2018, and December 31, 2024, for whom demographic data, anthropometric measurements, and FibroScan-based CAP values were available. In total, 430 patients aged between 18 and 74 years were included.

Inclusion and Exclusion Criteria

Adults aged 18–74 years with recorded height, weight, and WC measurements, as well as adequate and valid CAP data from FibroScan evaluations, were included in the study. Individuals were excluded if they were younger than 18 or older than 74 years; consumed alcohol exceeding 210 g/week (men) or 140 g/week (women); were pregnant; or had a history of hepatitis B, hepatitis C, autoimmune hepatitis, acute hepatitis, primary or secondary cholestatic liver disease, hemochromatosis or other metabolic liver disorders, liver cirrhosis, or malignancy.

Anthropometric and Clinical Measurements

Demographic data (age, sex) and standardized anthropometric measurements (height, weight, WC) were obtained retrospectively from the hospital information system and FibroScan device registry. BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). WHtR was determined by dividing WC by height in centimeters.

ABSI and BRI were calculated according to the following formulas:

ABSI= WC / (BMI$^{2/3}$ x height$^{1/2}$)

$$BRI = 364.2 - 365.5\sqrt{1 - \left(\frac{\text{waist circumference}}{\pi \times \text{height}}\right)^2}$$

Radiological Assessments

This study retrospectively analyzed patient records from individuals diagnosed with NAFLD via the FibroScan device. Hepatic steatosis was evaluated using a FibroScan 502 Touch model (Echosens, Paris, France) to obtain CAP values. Measurements were performed with either an M or XL probe, and the degree of liver steatosis was recorded in decibels per meter (dB/m). Data from patients with at least 10 valid measurements and a median measurement quality of less than 30% variability were deemed suitable for analysis.

To define hepatic steatosis, a CAP threshold of 257 dB/m or higher, as determined in the biopsy-controlled study by Yılmaz et al.[23], was employed. In that investigation, this cutoff was shown to distinguish marked hepatosteatosis with 89% sensitivity and 83% specificity (AUROC: 0.93).

Statistical Analysis

All statistical procedures were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was initially assessed via the Kolmogorov-Smirnov test. Variables following a normal distribution were presented as mean±standard deviation and compared using the independent samples t-test. Non-normally distributed data were expressed as median (minimum-maximum) and analyzed using the Mann-Whitney U test. Categorical variables were compared using the Chi-square test, and results were reported as frequencies and percentages.

A receiver operating characteristic (ROC) curve analysis was carried out to determine the diagnostic performance of each anthropometric measure used to detect NAFLD. The area under the ROC curve (AUC) was calculated for body weight, BMI, WC, WHtR, ABSI, and BRI. Higher AUC values indicated greater discriminatory power for diagnosing NAFLD. DeLong's test was used for pairwise comparisons of AUCs. Statistical significance was defined as a two-tailed p-value <0.05.

Based on the findings, the measure with the highest AUC had the strongest predictive capacity, while indices with lower AUC values were considered to have limited clinical utility. Subgroup analyses (e.g., sex differences) were also conducted when applicable.

To determine whether the differences in AUC values among the anthropometric indices were statistically significant, pairwise AUC comparisons were performed using the DeLong test. The DeLong test is a non-parametric method specifically designed to compare correlated ROC curves and provides a p-value indicating whether the difference between two AUC values is statistically significant. The significance level was set at p<0.05.

RESULTS

A total of 430 participants were included in this study, with 334 classified as having fatty liver and 96 as non-fatty liver. The demographic and clinical characteristics of the two groups are presented in **Table 1**.

Table 1. Comparison of demographics between the groups

	Non-fatty liver (n=96)		Fatty liver (n=334)		p
	Mean±SD	Median(min-max)	Mean±SD	Median(min-max)	
Age, years	48.17±13.7	48(20-74)	47.49±11.99	48(18-74)	0.661*
Gender Female, n (%) Male, n (%)		48 (50) 48 (50)		97 (29) 237 (71)	<0.001
Height, cm	167.08±11.39	168(115-189)	172.73±10.11	174(148-196)	<0.001
Weight, kg	77.3±12.02	76.5(50-114)	95.33±51.09	90(56-968)	<0.001
WC, cm	100.54±11.29	103(70-123)	110.03±12.5	108(79-152)	<0.001
ABSI Score	1.1±1.65	1.03(-4.13-9.7)	1.02±1.34	1.02(-6.08-8.04)	0.645
BMI, kg/m²	27.9±5.38	27.49(19.23-65.03)	32.1±20.96	30.47(18.94-402.91)	<0.001
BRI	5.69±2.11	5.3(2.31-16.05)	6.43±1.87	6.04(2.37-14.73)	<0.001
WHtR	0.60±0.08	0.59 (0.44-0.96	0.63±0.07	0.62 (0.44-0.92)	<0.001
CAP, dB/m	223.58±35.63	234(3.4-257)	324.26±34.36	325(258-400)	<0.001
LSM, kPa	8.51±9.2	5.3(2.6-75)	9.31±7.74	6.8(2.4-69.1)	<0.001

SD: Standard deviation, WC: Waist circumference, ABSI: A body shape index, BMI: Body-mass index, BRI: Body roundness index, WHtR: Waist to height ratio, CAP: Controlled attenuated parameter, LSM: Liver stiffness measurement, *: student t-test

Demographic and Anthropometric Comparisons

The mean age of the fatty liver group was 47.49±11.99 years, while the non-fatty liver group had a mean age of 48.17±13.7 years (p=0.661). A significant gender difference was observed between the groups, with a higher proportion of males in the fatty liver group (71%) compared to the non-fatty liver group (50%) (p<0.001).

Key anthropometric variables such as height, weight, WC, BMI, BRI, and WHtR demonstrated significant differences between the groups. The fatty liver group exhibited higher mean WC (110.03±12.5 cm vs. 100.54±11.29 cm, p<0.001), BMI (32.1±20.96 kg/m² vs. 27.9±5.38 kg/m², p<0.001), and WHtR (0.63±0.07 vs. 0.60±0.08, p<0.001). Similarly, weight and BRI were significantly elevated in the fatty liver group.

ROC Curve Analysis

ROC curve analyses were performed to evaluate the predictive power of various anthropometric measures for fatty liver diagnosis (Figure 1). Among the examined indices, body weight demonstrated the highest discriminatory power, with an AUC of 0.766 (95% CI: 0.716–0.816, p<0.001), followed by BMI (AUC=0.695, 95% CI: 0.637–0.753, p<0.001) and WC (AUC=0.693, 95% CI: 0.636–0.750, p<0.001), both of which showed moderate predictive accuracy. Conversely, WHtR and BRI exhibited lower discriminative ability with identical AUC values of 0.621 (95% CI: 0.554–0.688, p<0.001). The ABSI had the weakest predictive performance (AUC=0.485, 95% CI: 0.414–0.555, p=0.668), indicating that it was not useful for distinguishing NAFLD cases from controls.

The DeLong test was performed to compare the AUC values (Table 2) statistically. The results showed that body weight significantly outperformed all other indices (p<0.05 in all comparisons), confirming its superior predictive ability. BMI and WC performed similarly, as their AUC values were not significantly different (p=0.841). WHtR and BRI performed similarly (p=0.912), indicating neither provided superior discriminatory power. In contrast, ABSI was significantly inferior to all other indices (p<0.001 in all cases except

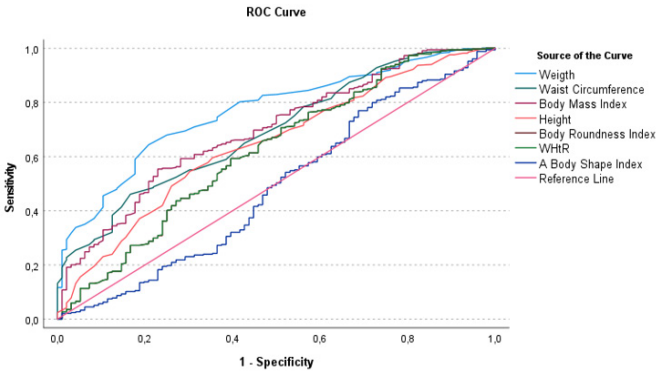

Figure 1. ROC curve analysis
ROC: Receiver operating characteristic

height), reinforcing its limited clinical utility. These findings suggest that body weight, BMI, and WC are the most effective anthropometric measures for NAFLD risk assessment, whereas ABSI lacks predictive value in this cohort.

Model Quality and Discriminative Metrics

The model quality scores, and classifier evaluation metrics are summarized in Table 3 and Table 4. Weight demonstrated the highest model quality (Gini index=0.532; Max K-S=0.435). WC (Gini index=0.387; Max K-S=0.294) and BMI (Gini index=0.390; Max K-S=0.325) also showed strong discriminative performance. WHtR had a moderate Gini index of 0.242 and a Max K-S value of 0.197.

Overall Model Quality

The overall model quality, shown in Figure 2, reaffirmed weight as the strongest predictor, with a quality score of 0.72. BMI and WC shared a quality score of 0.64, while WHtR and BRI had equally a lower model quality score of 0.55. ABSI had the lowest quality score (0.41), making it the least effective predictor among the variables analyzed.

DISCUSSION

Early and accurate detection of NAFLD is crucial for preventing the progression of chronic liver disease and related comorbid conditions. Hence, there is a pressing need

Table 2. Pairwise DeLong test p-values for AUC comparisons

Variable	Height	Weight	WC	BMI	BRI	WHtR	ABSI
Height	—	0.002*	0.051	0.038*	0.017*	0.019*	0.256
Weight	0.002*	—	0.006*	0.004*	0.002*	0.002*	<0.001*
WC	0.051	0.006*	—	0.841	0.093	0.042*	<0.001*
BMI	0.038*	0.004*	0.841	—	0.049*	0.018*	<0.001*
BRI	0.017*	0.002*	0.093	0.049*	—	0.912	<0.001*
WHtR	0.019*	0.002*	0.042*	0.018*	0.912	—	<0.001*
ABSI	0.256	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	—

AUC: Area under-the-curve, WC: Waist circumference, ABSI: A body shape index, BMI: Body-mass index, BRI: Body roundness index, WHtR: Waist to height ratio,*: Indicate statistically significant differences

Table 3. Area under the ROC curve

	Area	Std. error[a]	Asymptotic sig.[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Height, cm	0.644	0.032	0.000	0.582	0.706
Weight, kg	0.766	0.025	0.000	0.716	0.816
Waist circumference, cm	0.693	0.029	0.000	0.636	0.750
A body shape index	0.485	0.036	0.668	0.414	0.555
Body-mass index, kg/m^2	0.695	0.030	0.000	0.637	0.753
Body roundness index	0.621	0.034	0.000	0.554	0.688
Waist-to-height ratio	0.621	0.034	0.000	0.554	0.688

ROC: Receiver operating characteristic, a. Under the nonparametric assumption, b. Null hypothesis: true area=0.5

Table 4. Classifier evaluation metrics

	Gini index	K-S statistics	
		Max K-S[a]	Cutoff[b]
Height, cm	0.288	0.243	172.50
Weight, kg	0.532	0.435	85.500
Waist circumference, cm	0.387	0.294	109.500
A body shape index	-0.031	0.082	0.2931200000
Body-mass index, kg/m^2	0.390	0.325	29.7164
Body roundness index	0.242	0.197	5.5859
Waist-to-height ratio	0.242	0.197	0.6069

a. The maximum Kolmogorov-Smirnov (K-S) metric, b. In case of multiple cutoff values associated with max K-S, the largest one is reported

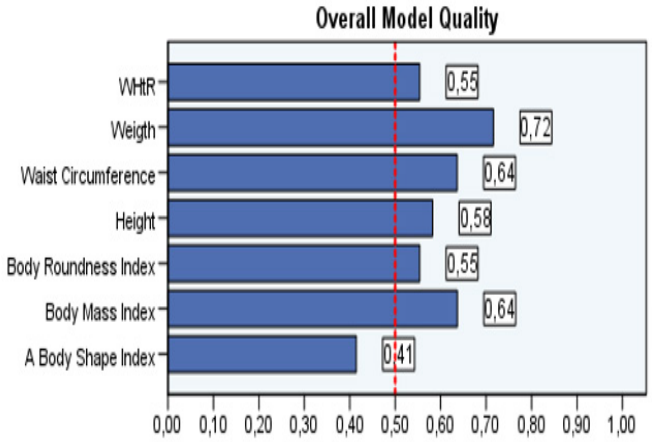

Figure 2. Overall model quality

for effective predictive indicators in clinical practice. In this study, we compared the predictive value of newly developed anthropometric indices with those of more traditional measures for NAFLD diagnosis. Earlier investigations suggested that age and sex might significantly influence NAFLD prevalence.[23,24] However, our findings showed no significant age difference between patients with and without fatty liver disease, indicating that age may not be a predictive factor in our cohort. Consistent with previous research showing that NAFLD predominantly affects males,[25] we also observed a higher prevalence among men in our study.

The observed gender disparity in NAFLD prevalence, with a higher occurrence in men (71% vs. 50%, p<0.001), aligns with current epidemiological findings and is influenced by hormonal, genetic, and metabolic factors. Several studies confirm that NAFLD is more prevalent in men than in premenopausal women due to the protective effects of estrogen, which helps regulate lipid metabolism and reduce hepatic fat accumulation. However, this protection diminishes after menopause, leading to an increased NAFLD risk in postmenopausal women.[26] A recent study analyzing transcriptomic differences suggests that immune responsiveness differs between men and women, with men showing an impaired liver regenerative response and increased inflammation.[27] Additionally, a meta-analysis revealed that while men are more likely to develop NAFLD, women—especially postmenopausal—experience more severe complications, including cardiovascular events.[28] These findings suggest that sex-specific screening and management strategies are essential for improving NAFLD outcomes in both men and women.

Numerous reports have highlighted a strong association between obesity and NAFLD, noting that this relationship persists in both early and advanced disease stages.[3,29,30] Common anthropometric indices, such as BMI and WC, have certain limitations, particularly in differentiating lean muscle mass from adipose tissue, thereby limiting their accuracy in predicting total body fat percentage.[31] Furthermore, visceral adiposity has been identified as the principal fat depot responsible for NAFLD, demonstrating a dose-dependent relationship with the disease.[32] Although robust correlations between conventional anthropometric measurements and NAFLD have been consistently reported, recent research has begun exploring new indices to evaluate their potential for distinguishing between patients with and without fatty liver disease.[33,34]

Thomas et al.[21] employed the BRI to estimate total and visceral adiposity. Previous studies likewise found that BRI holds promise as a clinical predictor for metabolic syndrome and is strongly correlated with NAFLD.[35,36] In another study by Tian et al.[37], transient elastography was used to determine CAP values, and BRI demonstrated superior diagnostic capability compared to BMI. Supporting these results, additional research has revealed that BRI and WHtR can exhibit high AUC values for diagnosing NAFLD.[36] However, our findings diverged from these reports by showing that BRI had a lower diagnostic value than body weight and BMI in identifying fatty liver.

Among the novel anthropometric indices, ABSI has been proposed as a potential predictor for conditions such as diabetes mellitus, cardiovascular disease, and hyperuricemia.[19-21] Nonetheless, a study investigating the relationship between ABSI and NAFLD reported insufficient predictive power for ABSI in diagnosing NAFLD.[37] Similarly, in a comparative analysis by Xie et al.[38] examining obesity-related indices for NAFLD detection, BMI emerged as the measure with the highest AUC. In contrast, ABSI, with an AUC of 0.578, failed to achieve adequate sensitivity and specificity. Another study also reported higher AUC values for BMI compared to ABSI and BRI.[39]

In our current study, measuring body weight yielded the most substantial predictive value for diagnosing NAFLD, followed closely by BMI and WC with similar predictive strengths. Meanwhile, BRI and WHtR possessed only modest predictive utility, and ABSI offered insufficient predictive accuracy for clinical use. Our findings align with other work suggesting that BRI and ABSI may lack adequate discriminatory power in differentiating fatty from non-fatty liver.[34]

Strengths and Limitations of the Study

Few studies have investigated the predictive utility of these newer anthropometric measures for diagnosing NAFLD in Turkish patients. Thus, our findings offer preliminary insights into whether these indices are suitable for this population. A notable strength is the relatively large sample size compared to prior reports. Additionally, NAFLD diagnosis was established using FibroScan-based CAP measurements, which are superior to conventional abdominal ultrasound.

Several limitations should also be acknowledged. First, this was a retrospective study. Second, comorbidities such as diabetes mellitus, hyperlipidemia, and hyperuricemias, as well as demographic factors like smoking history and physical activity—were not included in the analysis. Finally, although CAP measurements provide high sensitivity and specificity, the gold standard for NAFLD diagnosis remains liver biopsy, which was unavailable for our patient cohort; consequently, no histopathological comparison could be performed.

Limitations

One of the primary limitations of this study is the absence of data on comorbid conditions, particularly diabetes mellitus, which is a well-established risk factor for NAFLD. Diabetes is strongly associated with hepatic steatosis, insulin resistance, and disease progression, and its exclusion from the analysis may have influenced the predictive accuracy of anthropometric indices in diagnosing NAFLD. The interplay between metabolic disorders and NAFLD suggests that patients with diabetes might exhibit different anthropometric profiles, potentially altering the diagnostic performance of the indices evaluated. Future studies should incorporate detailed metabolic and comorbidity data to provide a more comprehensive understanding of their impact on NAFLD prevalence and severity.

CONCLUSION

In this cohort of Turkish patients diagnosed with NAFLD via Fibroscan, body weight emerged as the strongest predictor for detecting NAFLD, followed closely by BMI and WC, which showed similar predictive performance. By contrast, BRI and WHtR demonstrated limited utility, whereas ABSI appeared unsuitable for clinical implementation. Furthermore, these findings corroborate previous studies indicating a higher prevalence of NAFLD among male patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

University of Health Sciences, Bursa Faculty of Medicine, Bursa City Training and Research Hospital Ethics Committee Institutional Review Board (IRB) approved the study protocol (Date: 22.01.2025, Decision No: 2025-2/15).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Transition from emergency department to intensive care: the contribution of detailed anamnesis and early imaging to diagnosis and treatment processes

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ABSTRACT

Aims: The overcrowding of emergency departments (EDs) is a significant public health issue that diminishes the quality of healthcare services and increases mortality and morbidity rates both nationally and internationally. This study aims to emphasize the importance of detailed anamnesis and early bedside non-invasive imaging (ultrasonography) in patients transferred from the ED to the intensive care unit (ICU). It also addresses the impact of ED overcrowding on healthcare services and proposes solutions to enhance healthcare quality.

Methods: Between June 20, 2024, and November 25, 2024, patients over 18 years admitted to the ICU via the adult ED at Mardin Training and Research Hospital for various reasons were included in the study. A detailed anamnesis and non-invasive ultrasonographic imaging were performed for all ICU-admitted patients.

Results: Among the 242 patients admitted to the ICU, additional findings that influenced treatment decisions were identified in 21 patients through detailed anamnesis and imaging. Of these patients, 11 were male and 10 were female. The most frequent admission diagnoses were traffic accidents [8/21, (38.1%)] and respiratory distress [6/21, (28.6%)].

Conclusion: Our study demonstrates that performing detailed anamnesis and utilizing non-invasive imaging techniques in patients transferred from the ED to the ICU provides critical contributions to diagnosis and treatment. Strategies should be developed to reduce unnecessary ED visits and promote the appropriate use of emergency services.

Keywords: Emergency department, intensive care unit, ultrasonography, detailed anamnesis, echocardiography

INTRODUCTION

The overcrowding of emergency departments (ED) constitutes a significant public health issue that adversely affects the quality of healthcare services and leads to increased mortality and morbidity rates globally. This overcrowding has become a serious public health problem, preventing patients from receiving adequate health services and contributing to rising mortality and morbidity rates.[1,2] EDs are critical units in hospitals where patient stabilization and emergency care are provided. It is crucial to transfer critically ill patients to the intensive care unit (ICU) as quickly as possible, ensuring that the underlying issues are appropriately diagnosed. However, many patients who present to the ED do not require emergency intervention, which negatively affects access to care for critically ill patients and leads to diminished quality of healthcare services, resulting in misdiagnosis and inappropriate treatment.[3]

In the United States, the ratio of physicians to the population is 2.7 per 1.000 people, while the United Kingdom has 2.1, and Turkey reports 1.5.[4] The global average is 3.03. The high patient-to-physician ratio in EDs and the lack of qualified personnel limit the time available for patient assessment, negatively impacting diagnostic accuracy and treatment outcomes.[5]

The quality of care provided prior to admission to the ICU directly affects patient outcomes. A study by McQuillan et al.[6] reported significantly higher morbidity and mortality rates in patients who received inadequate care before ICU admission.

In recent years, learning and interpreting non-invasive imaging applications, especially ultrasonography (USG), has become an important area for physicians in the diagnosis, treatment and clinical observation processes of intensive care (IC) patients. In particular, the fact that USG and echocardiography can be performed at the bedside and non-invasively provides great advantages for patients.[7,8] The use of echocardiography as a non-invasive method in

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bedside evaluation of cardiovascular structures is of critical importance for IC patients and provides ease of use due to its portability.[9,10]

The goal of this study is to assess the negative effects of increased patient volume in EDs on healthcare services and to emphasize the importance of using non-invasive imaging methods like bedside USG and detailed anamnesis in improving early diagnosis, treatment, and clinical monitoring for patients admitted to the ICU.

METHODS

Ethics

The study was conducted with the permission of Mardin Artuklu University Non-interventional Clinical Researches Ethics Committee (Date: 11.06.2024, Decision No: 2024/6-1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

Between 20.06.2024 and 25.11.2024, patients over 18 years admitted to the ICU via the adult ED for various reasons were included in the study.

Study Environment

The study was conducted at Mardin Training and Research Hospital, which is a teaching hospital with a total capacity of 80 IC beds. The hospital has 38 adult ICU beds, 9 of which are designated for ICU. All ED patients were triaged by trained nurses. The ED staff includes emergency medicine specialists and resident doctors. Transfers to the ICU were made by consulting the ICU specialists during working hours and the on-duty specialists outside of working hours. When patients were admitted to the ICU, a detailed anamnesis was taken by the relevant specialist physician, along with bedside USG conducted, and any imaging that was lacking for the diagnosis was carried out.

Patient Selection

After obtaining ethical approval, patients admitted to the ICU between June 20, 2024, and November 25, 2024, were analyzed. Patients who were admitted directly from the ED to the ICU were included in the study.

The inclusion criteria were as follows: Adults over the age of 18 who were admitted directly to the ICU from the ED were included. Patients under 18 years of age, those transferred from other facilities, patients requiring postoperative IC, patients admitted to our clinic due to a need for IC from other departments, and patients transferred from other ICUs were excluded from our study.

Data Collection and Analysis

The patients admitted to the ICU from the ED between June 20, 2024, and November 25, 2024, were examined, and demographic and clinical data were collected and analyzed.

Statistical Analysis

The obtained data were analyzed using the SPSS software program. Descriptive statistics included frequencies and percentage distributions.

RESULTS

Between June 20 and November 25, 2024, a total of 158.000 patients from all departments presented to the ED, of which 242 critical patients were admitted to the 9-bed ICU. Among these, 21 patients were prospectively evaluated.

The most common complaints among patients admitted to the ICU from the ED were respiratory distress [34/242 (14%)], respiratory distress with altered general condition [7/242 (2.9%)], cardiac arrest [11/242 (4.5%)], gastrointestinal bleeding [11/242 (4.5%)], acute ischemic heart disease [11/242 (4.5%)], acute decompensated heart failure [6/242 (2.5%)], altered consciousness [15/242 (5.2%)], stroke [2/242 (0.8%)], dyspnea [7/242 (2.9%)], falls [6/242 (2.5%)], postoperative femur fracture [7/242 (2.9%)], and other causes [125/242 (52.8%)].

Of the admitted patients, 61 (25.2%) had no comorbidities, while 181 (74.8%) had at least one underlying condition. The most common comorbidities were hypertension [107/242 (42.2%)], type 2 diabetes mellitus [64/242 (26.6%)], chronic obstructive pulmonary disease (COPD) [30/242 (12.4%)], chronic kidney disease [27/242 (11.2%)], neurological disorders (Alzheimer's, dementia, epilepsy, Parkinson's disease, cerebrovascular accident) [50/242 (20.7%)], and coronary artery disease [46/242 (19%)].

Among these patients, 104 (43%) were female and 138 (57%) were male, with a mean age of 62.29±21.61 years. Patients with missed diagnoses had a mean age of 54.29±16.77 years (range: 24–78), with 11/21 (52.4%) male and 10/21 (47.6%) female.

The most frequent admission diagnoses were traffic accidents [8/21 (38.1%)], respiratory distress [6/21 (28.6%)], and other causes [7/21 (33.3%)], including abdominal pain (1), simple fall (1), gastrointestinal bleeding (1), cardiac arrest (1), liver disease (1), postoperative cesarean preeclampsia (1), and snake bite (1).

Table 1, 2 provide details on initial ICU admission diagnoses and general patient analysis.

Table 1. Patients' initial admission diagnoses to the intensive care unit

Admission diagnosis	Frequency	Percentage
Acute renal failure	1	4.8
Fall	1	4.8
Gastrointestinal bleeding	1	4.8
Ischemic heart disease	1	4.8
Liver disease	1	4.8
Postoperative cesarean preeclampsia	1	4.8
Respiratory distress	6	28.6
Traffic accident	8	38.1
Snake bite	1	4.8
Total	21	100

Percentage: %

Table 2. The general analysis of 21 patients evaluated in intensive care

Patient	Gender	Age	Reason for admission	Pre-existing conditions	Reason for ICU	Examination and imaging methods	Missed diagnosis (new diagnosis)	Procedure (treatment)
1	Male	42	Abdominal pain	None	Gastrointestinal bleeding	Abdominal ultrasound suspicious lesion	CT scan showed widespread mass	Further investigation and treatment were performed
2	Female	67	Nausea, vomiting, abdominal pain	Hypertension, diabetes mellitus	Acute kidney failure	Ultrasound showed full bladder	Catheter obstructed	Catheter irrigated
3	Female	65	Shortness of breath	Chronic kidney disease	Respiratory distress	Ultrasound showed full bladder	Catheter clamped	Clamp opened
4	Female	66	Shortness of breath, confusion	Hypertension, chronic obstructive pulmonary disease	Respiratory distress	Ultrasound showed full bladder	Catheter obstructed	Catheter replaced
5	Male	76	Fever, shortness of breath	Chronic kidney disease, chronic obstructive pulmonary disease	Respiratory distress	Ultrasound showed full bladder	Catheter obstructed	Catheter irrigated
6	Male	71	Shortness of breath, general weakness	Hypertension, diabetes mellitus	Respiratory distress	Ultrasound showed full bladder	No catheter	Urinary catheter inserted
7	Male	42	Road traffic accident	None	Road traffic accident	Tenderness in wrist	Direct radiograph showed radius fracture	Immobilized in a splint
8	Male	58	Snake bite	None	Snake bite	Wound on face	CT scan showed sphenoid fracture	Consulted with relevant specialist
9	Male	24	Shortness of breath, fever	None	Respiratory distress	Ultrasound showed pneumothorax	Confirmed by direct radiograph	Chest tube inserted
10	Female	37	Road traffic accident	None	Road traffic accident	Tenderness in wrist	Direct radiograph showed radius fracture	Immobilized in a splint
11	Male	28	Road traffic accident	None	Road traffic accident	Tenderness in hand	Direct radiograph showed finger fracture	Immobilized in a splint
12	Male	62	Road traffic accident	Hypertension, chronic obstructive pulmonary disease	Road traffic accident	Tenderness in foot	Direct radiograph showed fibula fracture	Immobilized in a splint
13	Male	41	Road traffic accident	Hypertension, diabetes mellitus	Road traffic accident	Swelling in toe	Toe fracture	Immobilized in a splint
14	Female	78	Shortness of breath, loss of appetite	Hypertension, diabetes mellitus	Respiratory distress, pneumonia	Pleural effusion, effusion: 20-25%	Patient was fluid overloaded and had abdominal pain	Fluid overload reduced
15	Female	34	Hypertension, pregnancy	Hypertension	Postoperative cesarean pre-eklampsia	Drug allergy	Incorrect drug identified	Drug changed
16	Female	72	Respiratory distress	Hypertension, diabetes mellitus, chronic kidney disease	Liver cirrhosis	Cardiac echo showed low EF, pleural effusion	Consulted with cardiology	Heart failure diagnosis
17	Male	75	Chest pain, loss of consciousness	Hypertension, chronic kidney disease	Ischemic heart disease+ chronic kidney disease	Substance use	Withdrawal syndrome	Consulted with psychiatry
18	Female	52	Road traffic accident	Hypertension	Road traffic accident	Back pain	CT scan showed T8 fracture	Steel corset applied
19	Female	38	Road traffic accident	None	Road traffic accident	Tenderness in forearm	Direct radiograph showed radius fracture	Immobilized in a splint
20	Female	54	Fall	None	Fall	Ultrasound showed fluid in abdomen	Splenic laceration	Followed up
21	Male	58	Road traffic accident	None	Road traffic accident	Swelling in nose	Nasal fracture	Treated by ENT department

CT: Computed tomography, ICU: Intensive care unit

The bedside ultrasonography (USG) results and treatments applied to the two evaluated sample patients are shown in **Figure 1, 2.**

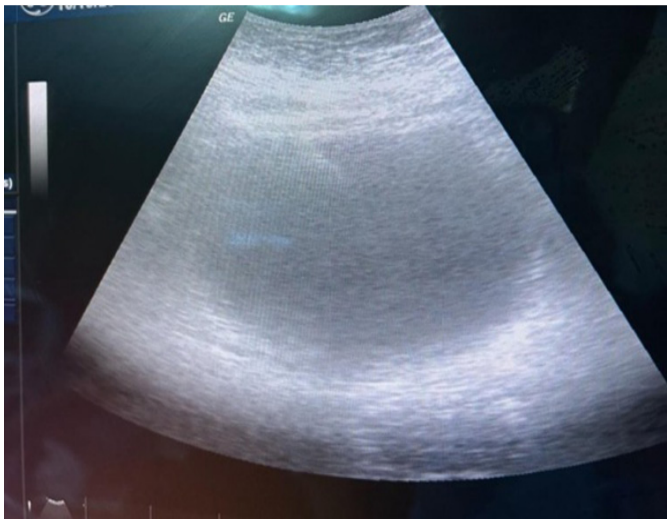

Figure 1. Female patient presenting to the emergency department due to respiratory failure

Figure 2. Male patient presenting to the emergency department due to respiratory distress

In one case, bedside ultrasound revealed a full bladder. The catheter was found to be blocked, and after flushing, 800 cc of urine was drained, leading to an improvement in respiratory distress and the discontinuation of diuretic therapy.

In another case, a patient admitted with pneumonia was diagnosed with pneumothorax via ultrasound. After a thoracic surgery consultation, a chest tube was placed, significantly improving respiratory status.

DISCUSSION

This study, which examined patients transferred from the ED to the ICU, identified missed diagnoses in 21 out of 242 patients (8.677%). In alignment with the literature, the rate of missed diagnoses in critically ill patients ranges between 8% and 10%, reaching up to 65% in complex cases.[11,12] Our findings are consistent with these reports, emphasizing the critical importance of early diagnosis and comprehensive patient assessment.

According to the 2011 World Health Organization (WHO) statistics, the number of physicians per 1.000 people was 2.7 in the United States, 2.1 in the United Kingdom, and 1.5 in Turkey, with a global average of 3.0. The increasing number of patients in EDs, combined with a shortage of qualified healthcare professionals, has led to a disproportionate physician-to-patient ratio. Consequently, the time allocated for thorough patient evaluation has significantly decreased, affecting the quality of emergency care.[4]

The misuse of ED services, an increase in ED visits, and a shortage of hospital beds contribute to ED and ICU overcrowding.[13,14] Delays in laboratory and radiology results, prolonged consultation times, and staff shortages further exacerbate this situation. Additionally, the growing population of critically ill patients, rising life expectancy, and an increase in comorbid diseases have led to prolonged hospital and ICU stays. Delayed diagnosis and misdiagnosis in the ED significantly increase mortality and morbidity rates.[15] Studies have demonstrated that ED overcrowding negatively impacts patient assessment, with delayed laboratory and radiological evaluations, prolonged consultations, and staff shortages hindering the timely diagnosis and management of critically ill patients.[15-17]

According to data from the National hospital ambulatory medical care survey (NHAMCS) in the United States, the average age of patients requiring ICU admission has been increasing over the years.[18] Aging is associated with an increased prevalence of chronic diseases, leading to higher rates of hospital admissions, including ICU stays.[19] In our study, the mean age of patients admitted to the ICU was 62 years, with a mean age of 66 years for females and 59 years for males, consistent with both national and global data. The aging population and the rising prevalence of chronic diseases continue to increase ICU admission rates.[17,19]

Recognizing the severity of illness early and ensuring optimal medical care for patients admitted directly to the ICU may contribute to reduced mortality rates. Some studies suggest that interventions before ICU admission are the most effective means of reducing ICU mortality, as once the underlying pathology becomes too severe or irreversible, ICU interventions may have limited impact on outcomes.[20] Based on this principle, our study incorporated detailed anamnesis, additional diagnostic tests, and imaging techniques to identify potentially missed diagnoses. As a result, 21 missed diagnoses were identified, corresponding to an 8.677% rate, which aligns with findings reported in the literature.

Among ICU admissions, the most common patient groups include trauma patients and those presenting with respiratory distress. In a study conducted in France by Fassier et al.[21], the most frequent reason for ICU admission was respiratory diseases, particularly acute pulmonary edema. Similarly, Flaatten et al.[22] reported that respiratory failure was the leading cause of ICU admission in patients aged 80 years and older. In our study, respiratory distress was the most common complaint among patients transferred from the ED to the ICU (34/242, 14%). Among the 21 missed diagnoses, respiratory distress was present in six patients (6/21, 28.6%).

Extremity injuries, fractures, and dislocations are among the most frequently overlooked diagnoses in the ED.[23-26] A study conducted in Finland reported that ICU admission due to trauma was more common in males than in females.[27] Diagnostic errors in the ED are predominantly related to fractures and/or dislocations (69%), making missed fractures a leading cause of malpractice claims in emergency medicine. According to the literature, musculoskeletal injuries are the most frequently missed diagnoses.[28,29] Guly, in a study analyzing 953 diagnostic cases, reported that the most frequently missed diagnoses involved hand and wrist injuries, followed by ankle fractures.[30] In our study, 8 out of the 21 missed diagnoses were related to traffic accidents, including 3 cases of radius fractures, 2 finger fractures, 1 fibula fracture, 1 T8 vertebral fracture, and 1 nasal fracture.

Early imaging techniques can facilitate rapid diagnosis and timely initiation of appropriate treatment for critically ill patients transferred from the ED to the ICU. Bedside USG and echocardiography play a crucial role in assessing hemodynamic status, enabling early diagnosis, and managing hemodynamically unstable patients.[7] Bedside echocardiography is particularly valuable in reducing complications during the transport of unstable patients.[9,10] In our study, two patients admitted to the ICU with liver cirrhosis and pneumonia were found to have reduced ejection fractions and pleural effusion using bedside echocardiography. Following cardiology consultation, appropriate fluid management was implemented, thereby preventing complications related to fluid overload.

The implementation of non-invasive bedside imaging techniques not only enhances diagnostic accuracy but also plays a pivotal role in patient management. USG is especially effective in detecting structural abnormalities within the chest wall and pleural lesions.[31] In our study, bedside USG enabled the early detection of pneumothorax in a patient admitted to the ICU with pneumonia. A prompt intervention following consultation with a specialist emphasized the significance of these imaging techniques in patient management. If the pneumothorax had been missed, the patient could have faced a life-threatening condition. In alignment with our findings, the literature supports the efficacy of bedside USG in diagnosing pneumonia, pleural effusion, and pneumothorax, as well as in reducing the risks associated with transporting hemodynamically unstable patients.[9,10,31]

Furthermore, in four patients admitted to the ICU with respiratory distress, bedside USG revealed full bladders due to low urine output. Three of these patients had blocked catheters, one had a clamped catheter, and one did not have a catheter inserted. Following catheterization or correction of catheter-related issues, the patients experienced symptomatic relief and a reduction in oxygen requirements.

A multicenter study in Spain on ICU admissions from EDs found that the most common comorbidities were hypertension, respiratory diseases, and diabetes mellitus. Differences in population demographics and lifestyle factors may account for variations in comorbidity patterns.[32] Our findings regarding patient comorbidities align with those reported by García-Gigorro et al.[32]

Limitations

Our study was conducted over a five-month period, and data were collected from 242 patients. The sample size is relatively small, which may limit the generalizability of our findings. In future studies, larger patient populations will be analyzed to further contribute to the existing literature.

CONCLUSION

A detailed evaluation of patients in the ED, along with the strategic use of early imaging techniques, improves diagnostic accuracy and accelerates the transition to the ICU. As emphasized in the literature, early diagnosis and timely intervention are critical in reducing mortality and morbidity rates. Our study highlights the importance of laboratory testing and imaging in critically ill patients requiring ICU admission. Non-invasive bedside imaging techniques serve as indispensable tools for enhancing diagnostic precision and improving treatment outcomes in the ICU. To enhance the quality of emergency care, it is essential to optimize resource allocation, increase personnel support, and expand the use of bedside USG.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Mardin Artuklu University Non-interventional Clinical Researches Ethics Committee (Date: 11.06.2024, Decision No: 2024/6-1).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Novel and traditional anthropometric indices to identify metabolic syndrome and metabolically healthy obesity in obese women

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ABSTRACT

Aims: Traditional anthropometric indices may be inadequate for distinguishing obese individuals with low metabolic risk or those who are metabolically healthy. Therefore, newer, innovative indices may offer improved diagnostic accuracy. Current study aims to evaluate effectiveness of both traditional and novel anthropometric indices in identifying metabolic syndrome (MetS) and assessing metabolic risk factors such serum uric acid (SUA) and atherogenic index of plasma (AIP).

Methods: This was a retrospective study involving data of 292 obese women. The patients were separated into groups according to presence of MetS and their SUA and AIP levels. Predictive power was estimated using receiver operating characteristic curves, by comparing the area under the curve (AUC).

Results: Our results showed that all novel indices except the weight-adjusted waist index (WWI) had potential utility in diagnosing MetS. The lipid accumulation product (LAP) index had the highest AUC for MetS diagnosis, with a value of 0.832 (95% CI: 0.783–0.880). The abdominal volume index (AVI) and waist-to-height ratio (WHtR) showed the highest sensitivity (82.3%), while the waist-triglyceride index (WTI) had the highest specificity (89%).

Conclusion: Notably, both the visceral adiposity index (VAI) and LAP index achieved specificity and sensitivity values exceeding 70% and can be used in MetS screening of obese women. In contrast, the WWI was found to be statistically insufficient for defining MetS and distinguishing between SUA and AIP groups.

Keywords: Uric acid, atherogenic index of plasma, obesity, metabolic syndrome

INTRODUCTION

Obesity, which is one of the components of the metabolic syndrome (MetS), contributes to the development of diseases such as cardiovascular disease (CVD), diabetes, musculoskeletal disorders, malignancies and neuropsychiatric disorders, and reduces life expectancy and quality of life.[1] However, the development of obesity-related comorbidities cannot be explained simply by the degree of obesity, and there is considerable variability among individuals. The observation that some obese individuals have a significantly lower risk of cardiometabolic abnormalities has led to the concept of metabolically healthy obesity (MHO).[2] Although there is no clear definition, the diagnosis of MHO is made in the literature simply by excluding the diagnosis of MetS in obese individuals.[2,3] In turn, it is simply explained by relatively lower visceral fat, higher subcutaneous and peripheral fat, and preserved insulin sensitivity and beta cell function compared to metabolically unhealthy obese individuals.[3,4]

Traditional criteria used in diagnosing obesity, such as waist circumference (WC), body weight, or body-mass index (BMI), may not consistently correlate with visceral fat mass. Although these measures are commonly employed in clinical practice due to their accessibility, they may not be the ideal methods for evaluating visceral obesity.[5] This has prompted a need for anthropometric indices that more accurately correlate with visceral fat mass and central obesity and that are associated with various cardio-metabolic factors, particularly MetS. Recent studies have explored this need, introducing innovative indices such as the conicity index (CI), A body shape index (ABSI), body roundness index (BRI), abdominal volume index (AVI), visceral adiposity index (VAI), lipid accumulation product (LAP) index, triglyceride-glucose (TGI) index, waist-triglyceride index (WTI), the Clínica Universidad de Navarra-Body Adiposity Estimator (CUN-BAE) equation, and the weight-adjusted waist index (WWI), among others, in the literature. These indices have been evaluated both individually and in combination, with studies investigating their associations with various conditions, including MetS parameters malignancy, and mortality.[6-14] Remarkable findings have been reported, highlighting their potential clinical relevance. However, further investigation is required to determine whether these novel anthropometric

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indices are superior to traditional metrics in detecting MetS, particularly among overweight or obese individuals, and to identify which indices may most closely correlate with MetS.

Several clinical studies have reported serum uric acid (SUA), the product of purine catabolism, and the atherogenic index of plasma (AIP), a strong marker of atherogenic dyslipidemia, as predictive markers of cardiovascular outcomes.[15,16] Both SUA and AIP are closely associated with MetS and its components.[17-21] The relationship of these cardiovascular risk markers, which have been strongly associated with MetS and CVD, to new anthropometric indices has not been clearly established, and there is also a scientific gap in this area. Therefore, this study was designed to reveal the association of traditional and novel anthropometric indices with MetS, SUA and AIP in obese adult women.

METHODS

The study was conducted with the approval of the Yalova University School of Medicine Non-invasive Clinical Researches Ethics Committee (Date: 08.01.2025, Decision No: 2024/362). All procedures adhered to ethical guidelines and the principles outlined in the Declaration of Helsinki. Since this was a retrospective study, written informed consent was not obtained from the patients.

The data of 292 adult female patients who were admitted to the obesity outpatient department with complaints of being overweight (BMI ≥30 kg/m^2) were retrospectively reviewed. Patients who were receiving medication for hyperuricemia or dyslipidemia, those older than 80 years or younger than 18 years, individuals with end-stage renal disease, pregnant patients, and those undergoing major surgery or hospitalized for any reason were excluded from the study.

The patients' age, height, weight, hip circumferences (HC), WC, and fasting biochemical values were recorded. Blood pressure was measured twice in the sitting position after at least five minutes of rest, and the mean values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were documented. Height and weight were measured with patients wearing minimal clothing and no shoes.

The diagnosis of MetS was established based on the modified National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria. However, for WC, the reference values of the Turkish Society of Endocrinology and Metabolism (≥90 cm for women) were applied. Accordingly, patients meeting at least three of the following criteria were classified as having MetS: increased WC, elevated serum triglyceride (TG) levels (≥150 mg/dl), reduced serum high-density lipoprotein cholesterol (HDL-Chol) levels (<50 mg/dl), elevated blood pressure (≥130/85 mmHg or a prior diagnosis/treatment for hypertension), and elevated fasting serum glucose levels (≥100 mg/dl or a prior diagnosis/treatment for diabetes).

The AIP was determined as the logarithmic ratio of TG to HDL-Chol.[16] As described in the literature, patients were divided into 3 groups according to their AIP value (AIP value less than <0.11, low risk; AIP value between 0.11 and 0.21, intermediate risk; and AIP value above 0.21, high risk of CVD).[16] Patients were divided into two groups according to their uric acid levels. The uric acid threshold was set at 6 mg/dl.

The formulas used for calculating anthropometric indices are provided in **Table 1**.

Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) formula=insulin (U/L)×glucose (mg/dl)/405.

Table 1. Formulas used in the calculation of anthropometric indices

- BMI=weight (kg)/height (m)^2
- CI=WC (m)/[0.109√{weight (kg)/height (m)}]
- ABSI=WC (m)/[BMI$^{2/3}$(kg/m^2) height$^{1/2}$ (m)]
- BRI=364.2−365.5×{1−[(WC(m)/2π)/(0.5×height (m))]^2}$^{0.5}$
- VAI=WC (cm)/(36.58+(1.89*BMI))x(TG/0.81)x(1.52/HDL-C) where TG and HDL are expressed in mmol/L
- LAP (for females)=(WC (cm)−58)xTG (mmol/L))
- AVI=[2x(WC (cm))^2+0.7x(WC (cm)−HC (cm))^2]/1.000
- TMI: weight (kg)/height^3 (m)
- TGI=Ln [fasting TG (mg/dl)×fasting glucose (mg/dl)]/2,
- WTI=Ln [fasting triglyceride (mg/dl)×WC (cm)/2]
- CUN-BAE was calculated using the equation body fat percentage (BF%)=−44.988+(0.503×age)+(10.689×sex)+(3.172×BMI)-(0.026×BMI^2)+(0.181×BMI×sex)−(0.02×BMI×age)−(0.005×BMI^2×sex)+(0.00021×BMI^2×age), where age is measured in years, and sex was codified as 0 for men and 1 for women
- WWI=WC (cm)/√weight (kg)
- WHR=WC (cm)/HC (cm)
- WHtR=WC (cm)/height (cm)

BMI: Body-mass index, CI: Conicity index, ABSI: A body shape index, BRI: Body roundness index, VAI: Visceral adiposity index (for females), LAP index: Lipid accumulation product index (for females), AVI: Abdominal volume index, TMI: Triponderal mass index, TGI: Triglyceride glucose index, WTI: Waist-triglyceride index, CUN-BAE: The Clínica Universidad de Navarra-Body Adiposity Estimator, WWI: Weight adjusted waist index, WHR: Waist to hip ratio, WHtR: Waist to height ratio, WC: Waist circumference, HC: Hip circumference, HDL-Chol: High density lipoprotein cholesterol, TG: Triglyceride

Statistical Analysis

The data analyses were performed using the Statistical Package for the Social Sciences for Windows, version 25.0 (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was employed to assess the normality of variable distributions. Descriptive statistics were presented as mean±standard deviation for normally distributed variables and as median with interquartile range for non-normally distributed variables. For group comparisons, the Student's t-test was used for normally distributed data, while the Mann-Whitney U test was applied to non-normally distributed data. Comparisons involving more than two groups were conducted using one-way ANOVA for parametric data and the Kruskal-Wallis test for nonparametric data. Correlation analyses were performed using the Spearman correlation test for nonparametric variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 292 obese women, with a mean age of 41.8 years, were enrolled in this study. The mean BMI of the participants was 37.96 kg/m^2, while the mean WC and HC were 106.4 cm and 127.4 cm, respectively. MetS was identified in 65.8% of the participants (n=192).

As expected, significant differences were observed in HDL-Chol, TG, AIP, glucose levels, glycosylated hemoglobin, HOMA-IR, SUA, SBP, DBP, WC, HC, and BMI when participants were stratified based on the presence of MetS.

Statistically significant differences were noted between the two groups for all evaluated anthropometric indices, except for the WWI. Detailed data are presented in Table 2.

Table 3 presents the results of the receiver operating characteristic (ROC) analysis, which was conducted to evaluate the predictive performance of anthropometric indices and equations for MetS in obese women. The analysis revealed that, except for the WWI, all equations and indices had an area under the curve (AUC) above 0.5 with statistically significant p-values, indicating their potential utility in diagnosing MetS in obese women. Among these, the highest AUC was observed for the LAP index. The highest sensitivity was found for the AVI and WHtR at 82.3%, whereas the highest specificity was observed for the WTI at 89%. The highest Youden index values were recorded for WTI (0.541) and LAP (0.536). Notably, both the VAI and LAP index demonstrated specificity and sensitivity exceeding 70%.

Bivariate correlation analysis between anthropometric indices, equations, and MetS status revealed the strongest correlation with the LAP index, while no significant correlation was found for WWI (Table 4).

Participants were further categorized into three groups based on their AIP, a key indicator of the atherogenic lipid profile that is closely associated with MetS. Statistically significant differences were observed between the groups in terms of CI, ABSI, VAI, LAP index, TGI, VTI, and WHR. However, no significant differences were found between the groups in classical anthropometric indices such as WC, HC, and BMI, nor in indices such as the BRI, AVI, TMI, CUN-BAE, WWI, and WHtR (Table 5).

Similarly, when participants were categorized into two groups based on SUA levels, no significant differences were observed in HC and WWI. However, statistically significant differences were found between the groups across all other examined

Table 2. Demographic, clinic and laboratory features of subjects according to presence of metabolic syndrome

Parameters	Patients without metabolic syndrome n=100	Patients with metabolic syndrome n=192	p-value
Age (years)**	42 (32-47.8)	44 (36-50)	0.051
T-Chol (mg/dl) *	192.5±35.7	197.3±37.1	0.288
HDL-Chol (mg/dl) **	53 (47-60.8)	46.5 (41-53)	<0.001
LDL-Chol (mg/dl) **	123.5 (105-139.8)	128 (109-146.5)	0.215
TG (mg/dl) **	104.5 (77-132)	153 (111.3-199.8)	<0.001
AIP*	-0.075±0.190	0.156±0.218	<0.001
Glucose (mg/dl) **	89.5 (85-95)	96 (89-107)	<0.001
HbA1c (%) **	5.4 (5.2-5.6)	5.7 (5.5-6.1)	<0.001
HOMA-IR**	2.31 (1.47-3.41)	3.85 (2.41-5.92)	<0.001
Creatinine (mg/dl) **	0.75 (0.71-0.81)	0.76 (0.69-0.82)	0.872
Uric acid (mg/dl) **	4.8 (3.9-5.3)	5 (4.3-5.8)	0.009
TSH (mIU/L) **	2.31 (1.51-3.31)	2.28 (1.49-3.25)	0.897
Systolic BP (mmHg)**	110 (110-120)	120 (120-140)	<0.001
Diastolic BP (mmHg)**	70 (60-77.5)	80 (70-90)	<0.001
Waist circumference (cm) **	99 (95-106)	109 (102.3-116)	<0.001
Hip circumference (cm) **	124.5 (118.3-130)	127 (121-136)	0.06
BMI (kg/m^2) **	36.07 (32.5-38.7)	38.53 (35.5-41.8)	<0.001
CI**	1.217 (1.171-1.253)	1.274 (1.230-1.319)	<0.001
ABSI*	0.073±0.005	0.076±0.004	<0.001
BRI**	5.973 (5.494-6.417)	6.642 (6.107-7.181)	<0.001
VAI**	1.523 (1.071-2.051)	2.678 (1.956-3.606)	<0.001
LAP index**	48.637 (34.652-62.930)	90.557 (64.110-117.190)	<0.001
AVI**	20.153 (18.587-22.781)	23.992 (21.3415-27.333)	<0.001
TMI**	22.523 (19.987-24.601)	23.996 (21.871-26.058)	<0.001
TGI**	8.449 (8.133-8.703)	8.871 (8.629-9.288)	<0.001
WTI*	8.522±0.3945	9.038±0.457	<0.001
CUN-BAE*	48.006±4.323	50.431±3.963	<0.001
WWI*	0.549±0.049	0.555±0.0509	0.327
WHR*	0.804±0.0592	0.853±0.054	<0.001
WHtR**	0.619 (0.592-0.664)	0.676 (0.640-0.720)	<0.001

T-Chol: Total cholesterol, HDL-Chol: High density lipoprotein cholesterol, LDL-Chol: Low density lipoprotein cholesterol, TG: Triglyceride, AIP: Atherogenic index of plasma, HbA1c: Glycosylated hemoglobin, HOMA-IR: Homeostatic model assessment for insulin resistance, TSH: Thyroid-stimulating hormone, BP: Blood pressure, BMI: Body-mass index, CI: Conicity index, ABSI: A body shape index, BRI: Body roundness index, VAI: Visceral adiposity index (for females), LAP index: Lipid accumulation product index (for females), AVI: Abdominal volume index, TMI: Triponderal mass index, TGI: Triglyceride glucose index, WTI: Waist-triglyceride index, CUN-BAE: The Clínica Universidad de Navarra-Body Adiposity Estimator, WWI: Weight adjusted waist index, WHR: Waist to hip ratio, WHtR: Waist to height ratio, * Independent sample t test (mean±SD), ** Mann-Whitney U test [median (IQR)].

Table 3. Area under the receiver operating curve for anthropometric indices in predicting of metabolic syndrome in obese women

Parameters	AUC (95% CI)	p value	Cut-off value	Sensitivity	Specificity	Youden index
CI	0.749 (0.69-0.808)	<0.001	1.263	57.8	85	0.428
ABSI	0.673 (0.608-0.738)	<0.001	0.0755	51	75	0.260
BRI	0.715 (0.651-0.778)	<0.001	6.088	76	63	0.390
VAI	0.800 (0.748-0.851)	<0.001	2.063	72.4	77	0.494
LAP index	0.832 (0.783-0.880)	<0.001	63.201	77.6	76	0.536
AVI	0.749 (0.689-0.808)	<0.001	20.683	82.3	57	0.393
TMI	0.641 (0.574-0.709)	<0.001	23.833	54.7	69	0.237
TGI	0.801 (0.751-0.852)	<0.001	8.730	67.7	79	0.467
WTI	0.810 (0.759-0.86)	<0.001	8.904	65.1	89	0.541
CUN-BAE	0.665 (0.599-0.732)	<0.001	49.821	60.9	66	0.269
WWI	0.528 (0.458-0.598)	0,432	0.537	65.6	42	0.076
WHR	0.735 (0.675-0.794)	<0.001	0.819	76	60	0.360
WHtR	0.750 (0.69-0.81)	<0.001	0.632	82.3	58	0.403
BMI	0.661 (0.595-0.727)	<0.001	36.947	64.6	64	0.286

AUC: Area under curve, 95% CI: Asymptotic 95% confidence interval, lower and upper bound, CI: Conicity index, ABSI: A body shape index, BRI: Body roundness index, VAI: Visceral adiposity index (for females), LAP index: Lipid accumulation product index (for females), AVI: Abdominal volume index, TMI: Triponderal mass index, TGI: Triglyceride glucose index, WTI: Waist-triglyceride index, CUN-BAE: The Clínica Universidad de Navarra-Body Adiposity Estimator; WWI: Weight adjusted waist index, WHR: Waist to hip ratio, WHtR: Waist to height ratio, BMI: Body-mass index

Table 4. Bivariate correlation results between metabolic syndrome and anthropometric indices

Parameters	Correlation coefficient (r_s)	p-value
CI	0.409**	<0.001
ABSI	0.284**	<0.001
BRI	0.353**	<0.001
VAI	0.492**	<0.001
LAP index	0.545**	<0.001
AVI	0.409**	<0.001
TMI	0.232**	<0.001
TGI	0.495**	<0.001
WTI	0.509**	<0.001
CUN-BAE	0.272**	<0.001
WWI	00.046	0.433
WHR	0.386**	<0.001
WHtR	0.411**	<0.001
BMI	0.265**	<0.001

CI: Conicity index, ABSI: A body shape index, BRI: Body roundness index, VAI: Visceral adiposity index (for females), LAP index: Lipid accumulation product index (for females), AVI: Abdominal volume index, TMI: Triponderal mass index, TGI: Triglyceride glucose index, WTI: Waist-triglyceride index, CUN-BAE: The Clínica Universidad de Navarra-Body Adiposity Estimator, WWI: Weight adjusted waist index, WHR: Waist to hip ratio, WHtR: Waist to height ratio, BMI: Body-mass index

indices and equations, including classical anthropometric indices such as WC and BMI (Table 6).

DISCUSSION

Considering the prevalence of obesity and its dramatic increase in recent decades, a realistic approach to reducing the medical and socioeconomic costs associated with obesity treatment may be to prioritize high-risk patients who would benefit most from weight loss interventions. Such risk-stratified obesity management will require better methods and strategies for quantifying the risk of obesity-related morbidity and mortality.

The relationship between traditional and novel anthropometric indices and MetS has been extensively investigated in the general population.[6-10]; however, studies focusing specifically on the obese population remain limited. In an study specifically using BRI and ABSI, BRI demonstrated the best ability to detect IR in the overweight and obese population, while only BRI and WC, but not ABSI, could significantly assess the presence of MetS.[11] The study conducted by Rasaei et al.[12] using ABSI and body composition analyzer data along with classical indices such as BMI, WC and neck circumference, they suggest that the largest area under the ROC curve was related to neck circumference, WC, fat mass and BMI not ABSI. In a study by Sagun et al.[22] using traditional indices and body composition analyzer, WC was not associated with MetS in overweight and obese individuals, but interestingly, forearm circumference was reported to be associated with MetS. In our detailed literature review, we did not find a study in which a wide range of innovative/novel anthropometric indices were used specifically in obese patients to define MetS or MHO. According to our results, the LAP index is the marker with the highest AUC value and VAI, which has both sensitivity and specificity rates above 70% together with LAP index, are indicies that may be successfully used to define MetS and differentiate MHO patients in obese individuals.

Circulating lipoprotein particles can be divided into many categories according to their size and density. Small dense LDL is more reactive to oxidation and is more closely associated with plaque formation, which causes atherosclerotic lesions, than large dense LDL. AIP is positively associated with small dense LDL, which has been shown to have a high predictive value for CVD.[16] AIP has a well-established link between MetS, obesity and BMI.[17-19] However, a specific study

Table 5. Demographic, clinic and laboratory features of subjects according to PAI groups

Parameters	Low risk group (AIP<0.11) (n=157)	Intermediate risk group (AIP=0.11-0.21) (n=54)	Increased risk group (AIP>0.21) (n=81)	p value
Age (years)**	43 (34.5-50)	41 (33-48.3)	43 (35.5-48.5)	0.610
T-Chol (mg/dl) *	193±32.5	188.5±33.5	205.5±43.9	0.012
HDL-Chol (mg/dl) *	54.0±9.6	44.8±6.2	44.7±7.8	<0.001
LDL-Chol (mg/dl) *	123.8±25.3	123.7±29.0	137.0±29.4	0.001
TG (mg/dl) **	100 (80-124)	148 (131-160.3)	220 (189-267)	<0.001
AIP**	-0.082(-0.197-0.030)	0.162 (0.135-0.185)	0.316 (0.251-0.413)	-
Glucose (mg/dl) **	94 (87-101)	91 (87-100.3)	95 (88-110)	0.211
HbA1c (%) **	5.5 (5.3-5.85)	5.6 (5.2-5.9)	5.7 (5.4-6.15)	0.021
HOMA-IR**	2.80 (1.73-4.26)	3.41 (2.12-4.58)	4.40 (2.38-6.78)	<0.001
Creatinine (mg/dl) **	0.76 (0.71-0.82)	0.75 (0.68-0.82)	0.76 (0.7-0.83)	0.853
Uric Acid (mg/dl) **	4.7 (3.8-5.2)	5.1 (4.5-5.8)	5.4 (4.6-6.2)	<0.001
TSH (mIU/L) **	2.41 (1.51-3.28)	2.37 (1.535-3.17)	2.11 (1.39-3.37)	0.677
Systolic BP (mmHg)**	120 (110-140)	120 (110-130)	120 (110-130)	0.916
Diastolic BP (mmHg)**	80 (70-80)	80 (67.5-80)	80 (70-80)	0.807
Waist circumference (cm)**	105 (97.5-111.5)	105 (100-114)	107 (100.5-114)	0.086
Hip circumference(cm) **	127 (120.5-135.5)	124 (120-133.3)	126 (120-135)	0.453
BMI (kg/m^2) **	37.4 (34.1-40.8)	37.5 (34.5-40.5)	38.1 (34.1-41.3)	0.868
CI**	1.24 (1.20-1.28)	1.26 (1.21-1.31)	1.28 (1.23-1.33)	0.001
ABSI*	0.074±0.004	0.075±0.004	0.076±0.004	0.003
BRI**	6.28 (5.78-6.94)	6.39 (5.90-7.11)	6.58 (6.04-7.06)	0.117
VAI**	1.532 (1.150-1.980)	2.687 (2.542-2.865)	3.939 (3.377-4.961)	<0.001
LAP index**	52.4756 (37.731-66.797)	78.059 (68.688-96.041)	124.517 (97.969-155.192)	<0.001
AVI**	22.33 (19.45-25.33)	22.34 (20.25-26.36)	23.23 (20.8-26.16)	0.116
TMI**	23.31 (20.99-25.69)	22.94 (20.79-25.93)	23.95(21.07-25.58)	0.853
TGI**	8.48 (8.23-8.67)	8.82 (8.74-8.93)	9.33(9.05-9.58)	<0.001
WTI**	8.58 (8.30-8.77)	8.98 (8.84-9.08)	9.41 (9.22-9.57)	<0.001
CUN-BAE*	49.57±4.18	49.42±4.19	49.78±4.44	0.887
WWI*	0.55±0.048	0.56±0.046	0.56±0.056	0.116
WHR**	0.83 (0.797-0.85)	0.84 (0.81-0.88)	0.86(0.81-0.89)	<0.001
WHtR**	0.65 (0.61-0.70)	0.66 (0.62-0.71)	0.67 (0.63-0.71)	0.087

T-Chol: Total cholesterol, HDL-Chol: High density lipoprotein cholesterol, LDL-Chol: Low density lipoprotein cholesterol, TG: Triglyceride, AIP: Atherogenic index of plasma ; HbA1c: Glycosylated hemoglobin, HOMA-IR: Homeostatic model assessment for insulin resistance, TSH: Thyroid-stimulating hormone, BP: Blood pressure, BMI: Body-mass index, CI: Conicity index, ABSI: A body shape index, BRI: Body roundness index, VAI: Visceral adiposity index (for females), LAP index: Lipid accumulation product index (for females), AVI: Abdominal volume index, TMI: Triponderal mass index, TGI: Triglyceride glucose index, WTI: Waist-triglyceride index, CUN-BAE: The Clinica Universidad de Navarra-Body Adiposity Estimator, WWI: Weight adjusted waist index, WHR: Waist to hip ratio, WHtR: Waist to height ratio. * One way ANOVA test (Mean±SD), ** Kruskal-Wallis test [median (IQR)].

evaluating the AIP among anthropometric indices, especially new innovative anthropometric indices, could not be identified despite an extensive literature search. Considering the results of our study, it should be noted that, after excluding innovative anthropometric indices using triglyceride-based data, the WHR, ABSI and CI created a significant difference between AIP risk groups, whereas traditional parameters such as BMI and WC parameters did not create a significant difference. When the indices that use TG in the calculation are included in the evaluation, the LAP index, VAI, TGI and WTI, in addition to WHR, ABSI and CI, also make a significant difference in the evaluation of AIP and we believe that these indices can be used in clinical processes.

Numerous studies have shown a significant correlation between serum UA, the end product of purine catabolism, and components of the MetS such as atherogenic lipid profile, obesity and hypertension.[20,21] Many possible reasons have been proposed to explain the association between hyperuricemia and MetS, such as reduced renal clearance or increased proximal tubular reabsorption of UA as a result of insulin resistance and elevated insulin levels, elevated leptin levels and fructose consumption, all of which are strongly associated with central obesity as the other components of MetS.[20,23] Studies on the relationship between anthropometric indices and SUA levels are relatively more than those conducted with AIP. The study by Hongwei et al.[24] used LAP, TGI, ABSI, cardiometabolic index, VAI, and BRI, and reported that the capacity of LAP and TGI indexes were better than other anthropometric indexes in predicting hyperuricemia. In a large sample study by Chen et al.[25], BMI, WC, BRI, WHtR, LAP, VAI, TGI, WTI, and WWI were all significantly associated with hyperuricemia. In the total population, WTI, and when the female and male populations were evaluated separately, LAP had the highest predictive power. In studies

Table 6. Demographic, clinic and laboratory features of subjects according to UA groups

Parameters	Group I Patients with normal uric acid values UA<6 (n =240)	Group II Patients with high uric acid values UA≥6 (n = 52)	p value
Age (years)**	43 (34.3-49)	43.5 (35-51.8)	0.577
T-Chol (mg/dl) **	189 (169-214)	194 (172.25-227.8)	0.275
HDL-Chol (mg/dl) **	50 (43-57)	47.5 (41-51.8)	0.046
LDL-Chol (mg/dl) **	125 (107.3-142)	130 (106.5-151.3)	0.288
TG (mg/dl) *	127 (93.3-169)	160.5 (103.8-229)	0.004
AIP**	0.055±0.230	0.178±0.238	0.001
Glucose (mg/dl) **	93 (87-101)	96.5 (88.3-107.8)	0.114
HbA1c (%) **	5.6 (5.3-5.9)	5.75 (5.4-6.2)	0.048
HOMA-IR**	3.12 (1.90-4.85)	4.20 (2.84-5.60)	0.010
Creatinine (mg/dl) **	0.75 (0.7-0.81)	0.78 (0.72-0.85)	0.152
Uric acid (mg/dl) **	4.7 (3.9-5.2)	6.5 (6.2-7.2)	-
TSH (mIU/L) **	2.32 (1.51-3.34)	2.275 (1.52-3.18)	0.880
Systolic BP (mmHg)**	120 (110-130)	120 (110-140)	0.195
Diastolic BP (mmHg)**	80 (70-80)	80 (70-80)	0.565
Waist circumference (cm)**	105 (99-112)	111.5 (104.3-116.8)	<0.001
Hip circumference(cm)**	126 (120-133)	127 (122-136.8)	0.167
BMI (kg/m^2)*	37.4 (33.7-40.4)	38.7 (36.6-44.9)	0.010
CI*	1.247±0.074	1.286±0.068	0.001
ABSI**	0.074±0.004	0.076±0.004	0.023
BRI**	6.264 (5.793-6.961)	6.756 (6.167-7.713)	0.001
VAI**	2.132 (1.409-2.905)	2.928 (1.949-4.136)	<0.001
LAP index**	67.226 (45.868-97.416)	98.257 (62.027-135.175)	<0.001
AVI**	22.316 (19.855-25.366)	24.938 (22.154-27.379)	<0.001
TMI**	23.156 (20.761-25.519)	24.365 (22.451-28.334)	0.013
TGI**	8.713 (8.411-8.970)	8.908 (8.511-9.375)	0.004
WTI*	8.812±0.485	9.092±0.507	<0.001
CUN-BAE*	49.296±4.195	51.003±4.216	0.008
WWI**	0.551±0.0500	0.558±0.0517	0.378
WHR**	0.832 (0.792-0.869)	0.862(0.823-0.889)	<0.001
WHtR**	0.651 (0.611-0.701)	0.692(0.653-0.736)	<0.001

T-Chol: Total cholesterol, HDL-Chol: High density lipoprotein cholesterol, LDL-Chol: Low density lipoprotein cholesterol, TG: Triglyceride, AIP: Atherogenic index of plasma, HbA1c: Glycosylated hemoglobin, HOMA-IR: Homeostatic model assessment for insulin resistance, TSH: Thyroid-stimulating hormone, BP: Blood pressure, BMI: Body-mass index, CI: Conicity index, ABSI: A body shape index, BRI: Body roundness index, VAI: Visceral adiposity index (for females), LAP index: Lipid accumulation product index (for females), AVI: Abdominal volume index, TMI: Triponderal mass index, TGI: Triglyceride glucose index, WTI: Waist-triglyceride index, CUN-BAE: The Clínica Universidad de Navarra-Body Adiposity Estimator, WWI: Weight adjusted waist index, WHR: Waist to hip ratio, WHtR: Waist to height ratio. * Independent sample t test (Mean ± SD), ** Mann-Whitney U test [median (IQR)].

with a narrower parameter range, the association of TGI, ABSI, and BRI with SUA has been demonstrated.[26,27] In our study, except for WWI and HC, both traditional and novel anthropometric indices showed statistically significant differences between groups according to SUA levels.

Limitations

Our study has several limitations. First, our study is a cross-sectional study. The cross-sectional, retrospective nature of our study does not allow us to establish a cause-and-effect relationship. The fact that only women were included in our study to form a homogeneous group and that it was a single-center study makes it difficult to extrapolate the results to the general population.

CONCLUSION

All anthropometric indices, except for WWI, were found to be effective in defining MetS. The LAP index demonstrated the highest AUC value. Both the VAI and LAP indices exhibited specificity and sensitivity exceeding 70%. Additionally, these indices showed a significant distinction between SUA and AIP risk groups. Simple calculation of LAP index and VAI can be used to identify obese women at high metabolic risk. In contrast, WWI was found to be statistically insufficient for both defining MetS and differentiating between SUA and AIP groups.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the approval of the Yalova University School of Medicine Non-invasive Clinical Researches Ethics Committee (Date: 08.01.2025, Decision No: 2024/362).

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

Referee Evaluation Process
Externally peer-reviewed.

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

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

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

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Original Article

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Risk factors for antibiotic-resistant respiratory infections among patients requiring ward admission

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ABSTRACT

Aims: The airway flora has been recognized as non-sterile, and sputum sampling is recommended for hospitalized patients with respiratory infections. Empiric antibiotic treatment is often initiated without culture confirmation, potentially contributing to antimicrobial resistance. This study aims to assess the influence of demographic factors, prior antibiotic use, and other risk factors on resistant respiratory cultures in ward-admitted patients.

Methods: A single-center cohort study was conducted in a pulmonary medicine ward of a tertiary hospital between the dates of March 2024 and September 2024. Patients over 18 years old with sputum, bronchoalveolar lavage (BAL), or endotracheal aspiration culture results were included. Demographic characteristics, comorbidities, vaccination status, prior infections, respiratory support needs, antibiotic history, and hospital admission records were collected. Nonparametric statistical analyses were used to evaluate associations, including the Mann-Whitney U and Kruskal-Wallis tests.

Results: Among 70 patients (mean age 68 ±9 years, 87% male), chronic obstructive pulmonary disease (COPD) (71.4%) was the most prevalent comorbidity. A total of 75.7% of cultures were from sputum samples, with *Pseudomonas* spp. (27.1%), *Klebsiella pneumoniae* (20%) and *Escherichia coli* (14.3%) being the most frequently isolated organisms. Resistant cultures were more common in patients with intensive care unit (ICU) admission history (p=0.007), intubation history (p=0.003), and non-invasive mechanical ventilation (NIMV) use (p=0.038). No correlation was found between prior antibiotic use and resistance.

Conclusion: ICU admission and respiratory support requirements were key risk factors for resistance. Contrary to previous studies, prior antibiotic use and comorbidities did not significantly impact resistance rates. These findings highlight the need for targeted antimicrobial stewardship and careful risk assessment among patients requiring pulmonary ward admission.

Keywords: Antimicrobial resistance, hospitalization, respiratory tract infections, risk factors

INTRODUCTION

The airway and its associated anatomical structures have been known to possess their own flora and are thus no longer assumed to be aseptic in nature. Guidelines suggest that while not mandatory for outpatient evaluations, sputum sampling should be performed for patients requiring inpatient care due to respiratory diseases.[1] While this suggestion remains especially important for patients with additional comorbidities and repeated admission history due to inadequate sampling, issues with sample care and transportation, patients being not suitable for sputum sampling or further invasive methods for airway sampling, in many cases, empiric treatment of respiratory infections is often initiated without a supporting culture result. Studies regarding possible causes of resistant culture originating from the respiratory tract remain an important topic, as respiratory infections remain the most common cause of infectious-related hospital admissions.[2]

Recent studies have shown that, over time, respiratory tract sampling results have been growing more resistant to standard treatment, with a higher sample count being reported.[3,4] In addition to being innate depending on the species, drug resistance is affected by environmental factors, including former antibiotherapy history and patient-related factors.[3] *Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Staphylococcus* spp. could be counted among commonly isolated samples with varying degrees of resistance. While originating from different families, the presence of resistant gram-positive coccus, pseudomonal, or actinobacteria spp. requires aggressive and specific treatment, with recommendations in place even for cases where a definitive culture with resistance could not be observed for patients with known risk factors.[5]

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Current guidelines and studies consider recent intensive care unit (ICU) admission, antibiotherapy history within three months, immunosuppressive states, and structural lung diseases as leading risk factors of resistant respiratory infection presence. Initially performed for pneumonia evaluation, similar studies have been performed for other underlying respiratory diseases, including chronic obstructive pulmonary disease (COPD). Pailhories et al.[3] stated that antibiotherapy regimens over time had changed the underlying microbiome in patients, with Zhao et al.[6] reporting similar findings in patients with cystic fibrosis.

In this study, we aimed to investigate the potential role of demographic parameters, former antibiotherapy regimens, and other risk factors on the resistant respiratory sampling results from patients requiring ward admission.

METHODS

The study was prepared as a single-center cohort study in the pulmonary medicine ward of a tertiary hospital. The study was conducted with the permission of the Scientific Studies Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date: 28.02.2024, Decision No: 2024-BÇEK/7). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study evaluated patients who were admitted to the pulmonary medicine ward between the dates of March 1, 2024 and September 1, 2024.

Patients who were over 18 years old and had at least one sputum, bronchial lavage, bronchoalveolar lavage (BAL), or endotracheal aspiration culture result were included in the study. Per the pulmonary medicine ward's routine testing, at least one sampling for sputum was performed for all patients unless other contraindicated, such as those with active hemoptysis. Exclusion criteria could be summarized as refusal to participate, inadequate patient information available due to the patient's wishes, and inadequate treatment duration in the ward, defined as a requirement for admission to another ward or ICU during the initial admission. Patients admitted for interventional procedures or additional pulmonary treatments which required admission such as chemotherapy were also removed from the study.

Patients' demographic characteristics, comorbidities, vaccination status, and history of smoking and alcohol were retrieved from the hospital records. Patients' infectious disease history, including former tuberculosis history, coronavirus disease 2019 (COVID-19) history, and any respiratory infection presence among caregivers, were also noted. Respiratory support requirements, including long-term oxygen support (LTOT) and non-invasive mechanical ventilation (NIMV), former antibiotic history within three months, and hospital admission status within a year prior to the study, were recorded from the national healthcare database. The definition of immunosuppressive treatment history included any treatment that was stated to be a treatment regimen equal to 20 mg methylprednisolone daily for at least 21 days. These statements and results were altogether present in a questionnare given to the patients, and was filled under the supervision of at least one pulmonary medicine specialist. The data present in the system and answers given to the questionnare were double-checked and any discrepancies were further validated with patients.

A culture result from respiratory tract sampling, which included sputum, bronchial lavage, BAL or endotracheal aspiration, was deemed positive if a specific bacteria or species were reported. A sample result was considered resistant if the culture was evaluated as resistant to high-use antibiotics for respiratory infections. A sample was deemed inadequate if inappropriate sampling was observed, such as above 10 epithelial cells per low power field for sputum sampling or contamination for BAL samples. If a sample was observed to be inadequate, that sample was removed from the study, and the patient was excluded from the study if the mentioned sample was the sole result of culture evaluation.

Total positive culture counts, including resistant culture counts, as a definition, included the count of culture that was observed during the patient's ward admission. The total positive culture count consists of any positive result, which includes the resistant samples. All analyses were performed separately for each group.

Statistical Analysis

The patients' results were put into a Microsoft Excel file for overall evaluation. After investigating any mis-input and values, the data were moved to a statistics module (IBM Version 25th for Windows). The initial assessment was performed by descriptive analysis, for which values were given with mean and standard deviation or with median and 25th to 75th percentiles as required. Parametric distribution was evaluated using a Q-Q plot analysis. Spearman's rho was utilized to analyze correlations between nonparametric scale variables. Mann-Whitney U test was used for nonparametric group comparison. Kruskal Wallis test was utilized for nonparametric comparison for groups with more than two nominal groups. P values at or below 0.05 were accepted as statistically significant. The study's sample size was calculated by G.Power 3.1.9.7. To evaluate a difference from the constant, due to the lack of a control group in the study by design; at least 53 patients were required to investigate an effect size of 0.5, with a type 1 error of 0.05% and power of 95%.

RESULTS

A total of 348 patients' admissions were investigated between the dates of March 1, 2024 and September 1, 2024. After the exclusion of repeated admissions (n=44), patients admitted due to chemotherapy regimens (n=120), patients admitted to ICU (n=19), and patients admitted to other wards (n=14), the remaining 151 patients were included in the study. Fourteen patients were excluded due to inadequate data, while 67 patients refused to participate in the study. The remaining 70 patients were accepted as the study population. Most of the patients were male (n=61), and the mean age was 68 (±9). Fifty-seven (81.4%) of the patients had a smoking history, with a mean smoking package/year of 51 (±29), and less than half of the patients had consumed alcohol regularly (n=31, 44.3%). COPD was the most prominent respiratory comorbidity (n=50, 71.4%), followed by lung carcinoma (n=17, 24.3%) and bronchiectasis (n=8, 11.4%). Other prevalent comorbidities

were hypertension (n=23, 32.9%) and diabetes mellitus (n=14, 20%). Twenty-five (35.7%) patients had a former COVID-19 history, 12 patients (17.1%) had a history of tuberculosis (including those treated for latent tuberculosis), and 16 patients (22.9%) had a former immunosuppressive treatment history. Six patients had a respiratory infection among caregivers or companions at home (Table 1).

Table 1. Demographic parameters and comorbidities

Parameters		**n (%)**
Gender	Male	61 (87.1)
	Female	9 (12.9)
Age (years, SD)		68 (9)
Smoking history	No	13 (18.6)
	Present	57 (81.4)
Smoking (package/year, SD)		51 (29)
Chronic obstructive pulmonary disease	No	20 (28.6)
	Present	50 (71.4)
Asthma	No	66 (94.3)
	Present	4 (5.7)
Bronchiectasis	No	62 (88.6)
	Present	8 (11.4)
Lung carcinoma	No	53 (75.7)
	Present	17 (24.3)
Interstitial lung disease	No	66 (94.3)
	Present	4 (5.7)
Hypertension	No	47 (67.1)
	Present	23 (32.9)
Coronary arterial disease	No	60 (85.7)
	Present	10 (14.3)
Congestive heart failure	No	64 (91.4)
	Present	6 (8.6)
Diabetes mellitus	No	56 (80)
	Present	14 (20)
Extrapulmonary malignancies	No	68 (97.1)
	Present	2 (2.9)
Alcohol	No	39 (55.7)
	Present	31 (44.3)
Tuberculosis history	No	58 (82.9)
	Present	12 (17.1)
COVID-19 history	No	45 (64.3)
	Present	25 (35.7)
Immunosuppressive treatment history	No	54 (77.1)
	Present	16 (22.9)
Respiratory infection among caregivers	No	64 (91.4)
	Present	6 (8.6)

SD: Standard deviation

Most patients were vaccinated for COVID-19 (n=67, 95.7%). Pneumococcal (n=28, 40%) and seasonal flu (n=38, 54.3%) vaccinations were also prevalent among patients. The majority of the patients (n=45, 64.3%) had been on LTOT, while 15 patients (21.4%) also required NIMV. Fifty-seven (81.4%) patients had at least one emergency ward admission history, with a median admission count of 3 (1-5) within a year. The median admission to a pulmonary medicine ward was reported to be 1 (0-2), with nearly half (n=37, 52.9%) of the patients requiring at least one admission. ICU history was present in 27 (38.6%) patients, with seven (10%) requiring intubation. Antibiotic usage within 3 months before admission was observed in 37 (52.9%) patients, with oral penicillin or cephalosporin regimens being the most reported antibiotic regimens (59.5%) (Table 2).

Table 2. Vaccination, respiratory support requirement, admission history and antibiotic usage of patients

Parameters		**n (%)**
Seasonal flu vaccination	No	32 (45.7)
	Performed	38 (54.3)
Pneumococcal vaccination	No	42 (60)
	Performed	28 (40)
COVID-19 vaccination	No	3 (4.3)
	Performed	67 (95.7)
Long term oxygen support	No	25 (35.7)
	Present	45 (64.3)
Non-invasive mechanical ventilation	No	55 (78.6)
	Present	15 (21.4)
Emergency ward admission history	No	13 (18.6)
	Yes	57 (81.4)
Emergency ward admission count (median, 25^{th}-75^{th})		3 (1-5)
Ward admission history	No	33 (47.1)
	Yes	37 (52.9)
Ward admission count (median, 25^{th}-75^{th})		1 (0-2)
Intensive care admission history	No	43 (61.4)
	Yes	27 (38.6)
Intubation history	No	63 (90)
	Yes	7 (10)
Antibiotic usage before admission	No	33 (47.1)
	Yes	37 (52.9)
Antibiotic regimen before admission	Oral penicillin or *Cephalosporin regimens*	22 (59.5)
	Macrolides	4 (10.8)
	Macrolides and oral penicillin/ Cephalosporin combination	7 (18.9)
	Respiratory fluoroquinolones	4 (10.8)

A median of 2 (1-3) positive culture counts with a median of one (1-2) count of resistant culture results were observed. Most cultures were from sputum samples (n=53, 75.7%). The most observed specimen in culture sampling was pseudomonas species (n=19, 27.1%), followed by Klebsiella pneumonia (n=14, 20%) and Escherichia coli (n=10, 14.3%). In correlation analysis, emergency ward admission count did not correlate with positive or resistant culture counts (p-value 0.243 and 0.120, respectively). Ward admission was observed to be weakly associated with resistant culture count (p-value 0.005 and correlation coefficient 0.329). However, no correlation

Table 3. Correlation between positive culture results and admission

Parameters		Positive culture count	Resistant culture count
Positive culture count (median, 25th-75th)			2 (1-3)
Resistant culture count (median, 25th-75th)			1 (1-2)
Sample origin	Sputum		53 (75.7)
	Lavage		14 (20)
	Endotracheal aspiration		3 (4.3)
Culture result	*Pseudomonas spp*		19 (27.1)
	Klebsiella pneumoniae		14 (20)
	Escherichia coli		10 (14.3)
	Enterobacteria spp		8 (11.4)
	Acinetobacter spp		4 (5.7)
	Moraxella catarrhalis		4 (5.7)
	Stenotrophomonas maltophilia		5 (7.1)
	Serratia spp		3 (4.3)
	Streptococcus pneumonia		1 (1.4)
	MRSA		1 (1.4)
	Haemophilus influenzae		1 (1.4)
Positive culture count	Correlation coefficient		0.804
	p value		0.001
Resistant culture count	Correlation coefficient	0.804	
	p value	0.001	
Emergency ward admission count	Correlation coefficient	0.141	0.188
	p value	0.243	0.120
Ward admission count	Correlation coefficient	0.221	0.329
	p value	0.066	0.005

spp: Species, MRSA: Methicillin resistant Staphylococcus aureus Spearman's Rho was used for correlation analysis

was observed with positive culture count (p-value 0.066) (Table 3).

Regarding culture count results, vaccination status, and former infectious disease history (tuberculosis and COVID-19) did not differ. Similarly, culture results did not vary according to comorbidities (Table 4).

Patients requiring NIMV support were observed to have a higher resistant culture count compared to those without (p-value 0.038); this observation was not present regarding the LTOT requirement. Intubation history affected both positive and resistant culture counts, as patients requiring intubation had a higher count in both groups (p-values 0.026 and 0.003, respectively). Patients with a history of ICU admission had a higher count of resistant culture sampling. However, a difference was not observed regarding the total positive culture count (p-values 0.007 and 0.149, respectively). Antibiotic usage before admission did not vary between groups (Table 4).

Resistant culture presence was found to be correlated with sample origin, with endotracheal sample results being more positive for resistance; however, the patient distribution within groups was not considered sufficient for analysis. Culture results and antibiotic regimen types did not affect the positive and resistant culture counts.

DISCUSSION

The study showed that ward admission was correlated, albeit weakly, with resistant culture counts, similar to ICU admission history, while other admission histories, including emergency ward admission, did not affect positive or resistant culture counts. Despite having a role in resistant culture results, ward admission and ICU admission history did not affect overall positive sampling. Comorbidities, a history of the former infectious disease, and antibiotic usage before admission also did not affect overall and resistant culture presence. Respiratory support requirement also had affected culture results, with patients requiring NIMV having a higher resistant culture count, while those with intubation history have a higher positive and resistant culture count. LTOT requirement was an exception, as patients did not vary in terms of culture results depending on oxygen support. These observations overall state that, for patients requiring pulmonary ward admission, different factors may contribute as risk factors to microbial resistance.

ICU admissions have been evaluated as a risk factor for resistance in bacterial isolates, with studies suggesting an increase in resistant sampling among patients in ICU units.[7] Former hospital admission was also shown as an additional risk factor for resistant sampling among ICU patients.[8] While

Table 4. Correlation between culture results and risk factors

Parameters		Positive culture count				Resistant culture count		
		n	Mean rank	Z	p	Mean rank	Z	p
Seasonal flu vaccination	No	32	35.59	-0.037	0.97	36.17	-0.3	0.764
	Performed	38	35.42			34.93		
Pneumococcal vaccination	No	42	34.13	0.729	0.466	32.87	1.568	0.117
	Performed	28	37.55			39.45		
Smoking history	No	13	36.5	-0.209	0.835	39.35	-0.894	0.371
	Present	57	35.27			34.62		
Alcohol	No	39	35.78	-0.138	0.891	37.47	-1.078	0.281
	Present	31	35.15			33.02		
Tuberculosis history	No	58	33.48	1.929	0.054	34.7	0.858	0.391
	Present	12	45.25			39.38		
COVID-19 history	No	45	33.56	1.135	0.257	34.1	0.914	0.361
	Present	25	39			38.02		
Immunsuppresive treatment history	No	54	35.48	0.015	0.988	35.09	0.364	0.716
	Present	16	35.56			36.88		
Long term oxygen support	No	25	30.92	1.485	0.138	30.28	1.893	0.058
	Present	45	38.04			38.4		
Non-invasive mechanical ventilation	No	55	33.57	1.605	0.108	33.27	2.075	0.038
	Present	15	42.57			43.67		
Chronic obstructive pulmonary disease	No	20	32.98	0.695	0.487	32.35	0.969	0.332
	Present	50	36.51			36.76		
Bronchiectasis	No	62	34.42	1.308	0.191	35.23	0.361	0.718
	Present	8	43.88			37.56		
Lung carcinoma	No	53	35.46	0.029	0.977	35.71	-0.178	0.858
	Present	17	35.62			34.85		
Hypertension	No	47	36.4	-0.562	0.574	36.1	-0.414	0.679
	Present	23	33.65			34.28		
Coronary arterial disease	No	60	35.69	-0.204	0.838	34.93	0.675	0.499
	Present	10	34.35			38.9		
Diabetes mellitus	No	56	35.82	-0.109	0.913	35.15	0.339	0.735
	Present	14	35			36.89		
Intensive care admission history	No	43	32.87	1.442	0.149	31.07	2.721	0.007
	Yes	27	39.69			42.56		
Entubation history	No	63	33.79	2.226	0.026	33.48	2.954	0.003
	Yes	7	50.86			53.71		
Antibiotic usage before admission	No	33	32.92	1.058	0.29	32.38	1.434	0.151
	Yes	37	37.8			38.28		

Z: Standardized Test Statistic. Independent Samples Mann-Whitney U test was utilized for the analysis.

ICU admission does not necessarily require a wide-spectrum regimen empirically, such as in pneumonia management, a history of ICU admission appears to be a risk factor for more resistant samples.[9] For *Pseudomonas aeruginosa*, this observation was stated in the study of Restrepo et al.[10], in which independent risk factors were reported for resistant *Pseudomonas aeruginosa* samples. All hospitalization history was stated to be a risk factor, in addition to COPD, indwelling catheter, and former respiratory infection history. Our study presents similar results and states that while ICU admission is a risk factor for resistant sampling, it does not increase the number of positive culture samples for patients admitted to the ward overall. Regarding ward admission, unlike ICU admission, studies remain limited, as most definitions were created with hospital admission in mind or included long-term facility care in addition to ward admission. Under these definitions, a review by Tacconelli[11] supports hospital admission within a year as a separate risk factor for resistant culture presence. Our results differ in these observations, as while ICU admissions remain a risk factor, other admissions were not considered a risk factor. This might be attributed to the respiratory nature of the study, as patients with other

comorbidities or those admitted due to non-respiratory causes may differ in resistance evaluation.

Microbial resistance is routinely attributed to former antibiotic usage, with even treatment regimens narrowed to a positive culture result, causing possible resistance later during the clinical course.[12] Former resistance culture presence has been reported as an area of interest, with one study recommending the exclusion of a drug that was reported to be resistant in a positive culture result within a year.[13] In our study, former treatment history or infectious disease history did not affect the positive or resistant sampling count. This could be attributed to the select patients of the pulmonary ward having different susceptibility or that, while the presence of a positive culture might be related, the culture count did not correlate well with the patients, especially those with respiratory comorbidities.

Vaccination history also did not correlate with microbial resistance in our study. Current literature supports vaccination's protective role in combatting possible resistance, especially in low-resource settings.[14] While our study did have patients with different vaccination histories and combinations of vaccines, a correlation could not be observed. This could be explained by patient selection, as those in the respiratory ward might be admitted due to pathogens that could not be targeted with vaccines, such as resistant species of Pseudomonas or Acinetobacter, as stated by the formerly referenced study and a review by Mishra et al.[14,15] Another factor could be that, while vaccination may protect against most commonly encountered pathogens, patients requiring admission to the pulmonary ward could have already been treated for these pathogens empirically before admission. Thus, an extensive treatment approach could have masked the protective role of vaccination.

An unexpected observation in our study was the lack of correlation between former treatment history and microbial resistance despite patients having a variety of former treatment histories. A possible contributing factor to this lack of correlation could be the exact duration of the former treatment and the general approach of abstaining from the same regimens upon admission. As stated by Kuster et al.[16], repeated treatment with the same regimen is often not chosen for the sake of possible underlying resistance, and the main component of failure, if such regimens were indeed chosen, would be the exact time of the former treatment. This exact time of former treatment, rather than the given range of three months, could have affected the presence of resistance; however, our study's design and difficulty of estimation of former treatment made the given range a more viable evaluation method.

Limitations

The study's main limitation was the patient population, in which more than 70% of the possible patients had to be excluded due to the study's design. While this was performed to evaluate the remaining patients better, excluding patients admitted for daily interventions, such as chemotherapy, might have caused a selection bias. However, including these patients could have caused unintentional issues, as patients admitted for treatment had already been screened for possible infectious processes and were also susceptible to infection as per the nature of underlying malignancy and immunosuppression from treatment regimens. Altogether, these factors would have affected the results. The detailed questionnaires also contributed to the limited patient pool, as patients and their caregivers had refused to participate in roughly half of the cases, with the majority of them stating that they would not be able to give adequate answers, were not sure if they could give correct answers, or refused to answer due to personal reasons. This also could be counted as a selection bias, as more cooperative patients had partaken in the study, naturally contributing to a larger study pool, while those with issues that limited this could not participate. As such, while we believe a reasonable estimation of possible risk factors was present in the study, patients with a lower socioeconomic and/or educational status may not be adequately represented. With a larger group of patients, we believe the results, at least regarding the pulmonary ward, would not have changed; however, a subgroup analysis, especially in the case of confirmed bacterial samples, such as Pseudomonas spp, could have been made.

CONCLUSION

Antibiotic resistance remains a topic of interest among patients admitted to the pulmonary ward. Risk factors contributing to resistant culture presence may not affect overall culture positivity. While the role of comorbidities and former treatment appears to be limited, sufficient demographic information, especially with the inclusion of former admission history and additional respiratory support requirements, appears to provide information regarding microbial resistance. As such, patients with these characteristics should be considered for possible resistance.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Scientific Studies Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date: 28.02.2024, Decision No: 2024-BÇEK/7).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Platelet indices: a new tool for monitoring infantile hemangioma treatment

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ABSTRACT

Aims: Infantile hemangioma (IH) is the most common benign vascular tumor in childhood. Diagnosis, treatment decision-making, and monitoring of the treatment are challenging. This study aims to investigate the utilization of platelet (PLT) indices as a marker in the follow-up of IH treatment.

Methods: The patients who were admitted and followed up in the outpatient clinic of Erciyes University Department of Pediatric Hematology and Oncology were enrolled in the study. The demographical data, treatment results, and PLT indices of the patients at certain time points were analyzed retrospectively. PLT, mean platelet volume (MPV), and platelet distribution width (PDW) were measured at various time points: upon admission, after the first and second months of treatment, at treatment completion, and during rebound episodes in affected patients.

Results: A general decrease in PLT, PDW, and MPV values was noted when comparing admission levels to the first month of treatment. The mean PLT count was 452.680/mm3 at admission, it decreased to 405.900/mm3 at the 1st month, 376.600/mm3 at the 2nd month and 359.900/mm3 at the end of treatment (p: 0,002). Besides MPV was evaluated, it was observed that while the mean was 10.43 fl at the time of admission, it decreased to 9.51 fl in the following months and the decline was statistically significant with a p value of 0,031. Lastly, regarding the mean PDW values, a decline was detected once again from 11.34 % to 10.2 % between the admission time and termination of the treatment with a statistically significant p value of <0.001.

Conclusion: Up to 15% of IH patients may require treatment due to complications. This study highlights that PLT, PDW, and MPV values can serve as valuable biomarkers for assessing treatment response and guiding clinical decision-making.

Keywords: Infantile hemangioma, platelet indices, propranolol treatment

INTRODUCTION

Hemangiomas are vascular tumors, which can be divided into two subgroups: infantile and congenital. Infantile hemangioma (IH) is the most common benign tumor in childhood, with a frequency of 5-12%.[1] Typically IH are not present at birth but arise in the first weeks of life exhibiting three unique evolutionary phases. On the other hand, congenital hemangiomas are rare and present at birth.

Some risk factors are determined according to the literature such as; prematurity, low birth weight, female gender, and multiple pregnancies.[2,3] The course of IHs is predictable, with three phases consisting of; proliferative, plateau, and involution. The proliferative phase can last until the age of 12 months followed by a plateau. The duration of the last phase may vary between 5- 12 years of age.[4] Only 5-10% of IF left scars, ulcers, or hyperpigmentation in the regression phase.[5]

Owing to the heterogeneous nature of the IH course, the necessity of treatment should be assessed carefully. The clinicians and family should be aware of the natural course and determine a risk/ benefit ratio. High-risk lesions should be evaluated and treatment options should be considered in terms of treatment results, prognosis, and impairment caused by the lesion. The most common choice of medical treatment is oral propranolol since discovered in 2008.[6,7] However, still, the timing of the termination of propranolol and tools that can be helpful for follow-up is still unclear. The main purpose of the current study is to investigate the use of platelet indices as a traceable, innovative, and non-invasive biomarker when evaluating the efficacy of propranolol in the treatment of IHs.

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METHODS

The study was conducted with the permission of Erciyes University Health Sciences Researches Ethics Committee (Date: 05.02.2025, Decision No: 2025/54). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In the current retrospective cohort study, medical records of the patients who were admitted to Erciyes University Pediatric Hematology and Oncology outpatient clinic between January 2021 and December 2024 and diagnosed with IH were evaluated. Of these 142 patients; topical treatment was initiated for 18 of them and these patients were excluded. The remaining 124 patients who received systemic propranolol treatment were enrolled. Age, gender, complaints on admission, location of the lesion, and platelet indices at certain time points of treatment were assessed. Platelet count (PLT), mean platelet volume (MPV), and platelet distribution width (PDW) were determined at admission, in the first month of treatment, in the second month, at the end of treatment, and at the time of rebound in patients with rebound. The changes in mean and median values of platelet indices between these time points were interpreted.

Statistical Analysis

In the present study, clinical results were evaluated using descriptive statistical methods. The quantitative characteristics of the patients are shown with numbers (n) and frequencies (%) in the text and tables. Descriptive statistics; number and percentage for categorical variables; For numerical variables, data that provided normal distribution parameters were given as mean±standard deviation, and for data that did not comply with normal distribution, they were given as median (minimum-maximum value). Comparison of data was made with Student's t-test for variables with normal distribution, and with Mann-Whitney U test for those with non-normal distribution. Besides, an ANOVA test was performed to compare the multiple parametric results in dependent groups.

RESULTS

Of the 124 patients enrolled, 25.8% (n: 32) were male and 74.2% (n:92) female. The mean age on admission was 4.47±2.9 months and the median was 3.75 months (minimum 15 days-maximum 15 months). The mean time of diagnosis by the family doctor or a pediatrician was 1±0.8 months. 25.8% (n: 32) of patients had superficial lesions, 50.8% (n: 63) had mixed lesions, and 23.3% (n:29) had deep IH lesions. Regarding the location of IH lesions; the most common site was the head-neck region with 46.7% (n: 58). Of these patients, 18.9% (n: 11) originated from the periocular area. 38 patients (30.6%) had ulcerated lesions. Of them, 39.4% (n: 15) originated from the head-neck region while the remaining 34.2% (n:13) from the extremity and 26.3% (n:10) from the genital region. Demographical findings are available in Table 1.

Table 1. Demographical findings of patients with infantile hemangiomas

	n (%)
Sex	
Female	n: 92 (74,.2%)
Male	n: 32 (25.8%)
Age on admission (months)	
Mean±SD	4.47±2.9 months
Median (min-max)	3.75 months (min 15 days-max 15 months)
Lesion type	
Superficial lesions	n:32 (25.8%)
Deep lesions	n:29 (23.3%)
Mixed lesions	n:63 (50.8%)
Location	
Head-neck	n:58 (46.7%)
Periocular	n:11 (18.9%)
Body	n:20 (16.1%)
Extremity	n:33 (26.6%)
Genital area	n:13 (10.4%)
Treatment duration time (months)	
Mean±SD	9.98±4 months
Median (min-max)	10 (min 1-max 21) months

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

83 patients (66.9%) were initiated peroral propranolol treatment at the age of ≤5 months. The dose of oral propranolol was initiated as 1 mg/kg/day and escalated to 2 mg/kg/day. The mean treatment duration was 9.98±4 months and the median was 10 months (minimum 1- maximum 21 months). The patient who had the treatment for 1 month, developed severe difficulty in breathing during the bronchiolitis period, and owing to this the treatment was terminated with the informed consent of the family. On the other hand, the patient who had the treatment for 21 months, had an ulcerated hemangioma originating from the extremity covering a large area. 54 patients (43.5%) are still on treatment. Regarding the side effects, a total of 48 patients (38.7%) had complaints during the propranolol treatment. The most common complaint was restlessness in 26 patients (54.1%), followed by loss of appetite and inability to gain weight in 21 patients (43.7%), and respiratory distress in only 1 patient (0.2%), whose treatment period was terminated early.

Platelet indices (PLT, MPV, PDW) were analyzed in certain time points described previously. Rebound growth of hemangioma was observed in only 21 (16.9%) patients. None of these patients restarted the treatment. Of them, only 7 patients had the PLT indices checked. Owing to the insufficient number, the rebound group was not enrolled in the statistical evaluation. The mean, median, standard deviation, and minimum-maximum values of PLT indices are available in Table 2. In terms of PLT, the mean value was initially 452.680/mm³ upon admission. Over the course of the treatment, this value progressively decreased, reaching 405.900/mm³ by the 1st month, 376.600/mm³ at the 2nd month, and 359.900/mm³ at the end of the treatment. This decline was statistically significant, with a p-value of 0.002, suggesting a notable reduction in PLT throughout the treatment period. Similarly, the mean value for MPV was observed to be 10.43 fl at the time of admission. As the treatment progressed, a consistent decrease was recorded, with the MPV value dropping to 9.51 fl in the subsequent months. The reduction in MPV was also found to be statistically significant, with a p-value of 0.031, indicating that MPV levels declined significantly during the treatment period. Lastly, regarding PDW, the mean value was 11.34% at admission, and it steadily decreased to 10.2% by the end of treatment. This change was highly statistically significant, with a p-value of <0.001, reinforcing the trend of

Table 2. Platelet indices on certain time points

	Admission	1st month	2nd month	Termination time	p-value
PLT (/mm³)					
Mean±SD	452.680±109.800	405.900±96.300	376.600±101.200	359.900±105.850	**p1:0.002**
Median (min-max)	441.000 (219.000-959.000)	394.000 (187.000-636.000)	373.000 (175.000-701.000)	336.000 (207.000-767.000)	**p2:0.045**
MPV (fl)					
Mean±SD	10.43±0.99	10.02±0.86	9.67±0.75	9.51±0.74	**p1: 0.031**
Median (min-max)	10.4 (7.8-12.8)	9.9 (8.4-12.8)	9.5 (8.3-11.8)	9.3 (8.3-11.4)	p2: 0.093
PDW (%)					
Mean±SD	11.34±2.21	10.94±1.7	10.55±1.63	10.2±1.51	**p1: <0.001**
Median (min-max)	11.4 (10.8-19.2)	10.8 (7.8-17.4)	10.3 (7.8-15.7)	9.8 (7.8-14.2)	**p2: <0.001**

SD: Standard deviation

a reduction in PDW throughout the treatment process. The difference for all the indices was statistically significant, with p values available in Table 2.

DISCUSSION

The present study evaluates the demographic characteristics, treatment responses, and side effects of oral propranolol in IHs. The significant decline observed in platelet indices during the first months of treatment suggests a potential hematological impact that warrants further investigation. These findings contribute to a better understanding of propranolol's effects and may guide future clinical management strategies.

IHs arise 2-5 times more frequently in girls than in boys.[1,2] In the present retrospective cohort, female patients were the majority which is in line with the literature. Regarding other demographic characteristics, the mean age on admission was 4.47 months which is important owing to the fact that the first 5 months is the upper limit of the opportunity window for initiating systemic treatment with propranolol, because IH lesions are in the proliferative period in this time period, full-filling the 80% of their growth.[8-10] On the other hand, the maximum age for admission was 15 months in our retrospective study. This patient has initiated treatment due to an ulcerated lesion and benefited. Based on this, it can be considered that the treatment decision should be evaluated individually and decided according to the area and condition of the lesion.

Regarding the evaluation of treatment necessity, the lesions should be classified as low-risk and high-risk. High-risk criteria consist of; the presence of life-threatening complications, functional loss, ulcers, PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac anomalies, eye anomalies), and permanent deformity.[5,6,11] Although there were no life-threatening events, the remaining criteria were judged at the onset of treatment in our study.

Propranolol is the gold standard in the treatment of IHs. The dosing is determined as beginning with 1 mg/kg/day and escalation to 2-3 mg/kg/day is recommended in the guidelines.[6,7,12] However, the recommended duration of the treatment can range between 6-12 months.[12,13] The mean treatment duration was 9.98±4 months in the present study which is similar to the literature. However, the range is between a minimum of 1 month to a maximum of 21 months. As mentioned earlier, the patient with the 1 month of treatment discontinued the drug owing to a life-threatening side effect. On the other hand, the patient who had the treatment for 21 months had an ulcerated lesion located in a large area on the extremity. Regarding these patients, it should be underlined that exceptions always exist and the treatment should be tailored to the needs of the lesion and the patient. Evaluating the treatment results and rebound rate, the present study had a rebound rate of 16.9 % (n:21), which seems to be less than the literature as reported before as 25%.[6,12,13] Also, 38.7% of our patients had reported a side effect. However, evaluating a complaint as a side effect is a challenging process in IH treatment, owing to some side effects being subjective, i.e. restlessness. The rate of side effects reported in the literature varies between 17% to 96%, which can be attributed to the same evaluation problem.[13,14]

The follow-up period of treatment, the escalation rate of the dosing, and the duration are still matters of debate. Clinicians need an objective and easily applicable tool to manage the treatment process. The pathogenesis of proliferation mainly depends on increased vascular endothelial growth factor (VEGF) release resulting in excessive angiogenesis, especially in the proliferative period.[15,16] Platelets also have a role in angiogenesis and interact with VEGF. Therefore, with sufficient treatment, the VEGF levels are expected to decline, leading to a decline in PLT indices, as described by Eroglu et al before in their study consisting of 22 patients.[17] As expected, a decline was observed in our study, between the admission and termination of the treatment in all of the PLT indices which are available in Table 2. Also, a statistically significant decrease was demonstrated in PDW and MPV values between the admission and termination times. These results can be attributed to the successful treatment and dosing.

The significant decrease observed in PLT, MPV, and PDW during the course of propranolol treatment in IHs suggests the hematological effect of the drug. The decline in PLT from 452.680/mm³ at admission to 359.900/mm³ at the end of treatment (p: 0.002) aligns with previous studies that have reported a reduction in platelet levels following propranolol administration in patients with hemangiomas. This phenomenon may be associated with the drug's vasoconstrictive properties, which could lead to a reduction in blood flow and, consequently, a decrease in platelet production or activity.[17-19] In addition, the statistically significant decrease in MPV from 10.43 fl to 9.51 fl (p: 0.031) supports the hypothesis that propranolol not only affects PLT but may also influence platelet size, indicating changes in platelet function. Previous literature has suggested that MPV can serve as an indicator of platelet activation, and a decrease

in MPV may reflect a reduction in platelet activation or an alteration in platelet production pathways.[17-20] Therefore, the reduction in MPV observed in our study may point to an overall change in platelet activity under the influence of propranolol. Furthermore, the decline in PDW from 11.34% to 10.2% ($p<0.001$) is another noteworthy finding. PDW is an indicator of platelet heterogeneity, and a reduction in this value has been linked to a decreased platelet response to injury or altered platelet function. The observed decrease in PDW may suggest that propranolol affects platelet maturation or their ability to respond to vascular damage, further supporting the drug's systemic effects.[17-21] These hematological changes underscore the importance of monitoring platelet indices during propranolol treatment, particularly in patients with IHs. While these findings are consistent with prior studies, the clinical significance of the changes in platelet indices remains unclear and warrants further investigation. Future studies should aim to elucidate the long-term impact of propranolol on platelet function and its potential implications for patient management.

Limitations

The major limitation of our study is its retrospective nature. Owing to this, the data about prematurity, and maternal and familial features could not be accessed. In addition to this, VEGF levels, which could have revealed the exact mechanism, were not measured. Besides, only the patients on systemic treatment were enrolled in the study. On account of this, the decline in the PLT indices can not be solely ascribed to the treatment success, because no other data in different groups were evaluated and compared. Lastly, to make these results more useful for clinicians, larger-scale studies should be performed with the aim of determining a cut-off point for PLT indices, enabling their use in daily clinical practice.

CONCLUSION

IHs generally undergo spontaneous regression. Nevertheless, up to 15% of the patients with IHs can develop complications leading need for treatment. In order to prevent unnecessary treatment and side effects, determining the lesions which actually need treatment and utilizing the appropriate treatment method is vital. Besides, monitoring the treatment results and deciding on timing are important issues for clinicians dealing with IHs. The present study disclosed that PLT, PDW, and MPV values can guide clinicians in evaluating treatment response.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Erciyes University Health Sciences Researches Ethics Committee (Date: 05.02.2025, Decision No: 2025/54).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Assessment of orbital injury in the emergency department

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ABSTRACT

Aims: Orbital injury is a significant clinical presentation in the emergency department (ED). This study aims to evaluate the clinical and radiological findings in patients presenting to the ED with orbital injury.

Methods: For patients who presented to the ED due to orbital injuries and underwent computed tomography scanning, data were recorded on age, gender, type of trauma, the presence of additional trauma locations (if any), the injured eye, the cause of injury, and the specific location of the injury.

Results: 314 patients were included in the study, with a mean age of 46.54±18.23 years (range: 18–79). Among these, 217 patients (69.1%) were male. Blunt trauma was observed in 202 patients (64.3%), and 102 patients (32.5%) sustained injuries as a result of road traffic accidents. Analysis of injury localization revealed that bone injuries were present in 202 patients (64.3%). Patients who experienced blunt trauma were significantly older ($p<0.001$). Individuals who suffered from falls from height and falls from the ground had higher mean ages compared to those with other injury types ($p<0.001$ for both comparisons). Patients involved in road traffic accidents were also found to be older than those with gunshot injuries ($p<0.05$). A gender-specific analysis indicated that, among females, road traffic accidents and falls from the ground were more prevalent, whereas males more frequently sustained gunshot injuries ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). Additionally, anterior chamber injuries were significantly more common in male patients ($p<0.001$).

Conclusion: The analysis indicates that the types and etiologies of orbital injury vary according to the patients' ages, while the patterns of injury differ based on gender.

Keywords: Orbital injury, emergency department, computed tomography

INTRODUCTION

The orbit represents an intricate anatomical structure that integrates complex structural, vascular, and functional attributes. It is defined as the osseous cavity within the cranial vault that accommodates the globe and its ancillary tissues. Morphologically, the orbital cavity exhibits a conical configuration, delineated by the anterior and middle cranial base in conjunction with the viscerocranium. It is anatomically bounded by four distinct osseous walls—namely, the superior (roof), inferior (floor), medial, and lateral walls—which confer structural integrity and provide critical protection to the eye.[1] Encompassed within this cavity are various soft tissue components, including the globe, extraocular musculature, adipose compartments, and the lacrimal apparatus, which collectively facilitate ocular motility, provide biomechanical cushioning, and sustain the physiological functions of the visual system.[2]

Orbital trauma constitutes approximately 3% of all presentations in the emergency department (ED).[3] Blunt orbital trauma describes injuries inflicted upon the orbital region as a result of significant impact forces, frequently leading to fractures of the orbital walls. Conversely, penetrating orbital trauma involves injuries to the orbit that occur without direct compromise of the ocular globe, often resulting from the incursion of either blunt or sharp objects, with the former typically imparting more extensive structural damage.

Orbital injury encompasses injuries to the orbital cavity, a region characterized by its limited spatial dimensions and the presence of critical neurovascular and muscular structures. Such injuries may involve osseous fractures or soft tissue damage, potentially concluding in adverse outcomes such as visual impairment or dysfunction of the extraocular muscles. Additionally, the presence of foreign bodies into the orbital space can precipitate significant pathological sequelae. The prevalence and severity of orbital injury depends on by a variety of factors, including the patient's age, the etiological

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mechanism of injury, and underlying socioeconomic determinants.

Efficient diagnosis and early therapeutic intervention are vital in the management of orbital injury. Radiographic evaluation is necessary for the conclusive diagnosis of orbital fractures. Currently, computed tomography (CT) is regarded as the gold standard in imaging, as it provides rapid, high-resolution details regarding the extent, and anatomical localization of orbital fractures, and associated soft tissue involvement, while also allowing comprehensive assessment of adjacent facial osseous structures for additional injuries.[4] The presence of orbital foreign bodies introduces significant diagnostic and therapeutic complexities, primarily owing to their often-subtle entry points. In these instances, CT imaging is critical, given its efficacy in identifying both metallic and non-metallic foreign materials.

The aim of the present study is to assess the clinical and radiological characteristics of patients presenting with orbital injury in the ED.

METHODS

The approval was granted by the Ministry of Health Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 29.01.2025, Decision No: 2025/0185). The study was retrospective, consent was not obtained from the participants. The study was conducted following the Declaration of Helsinki.

A retrospective analysis was conducted on patients aged 18 years or older who underwent orbital CT or maxillofacial imaging, as requested from the ED, between November 1, 2022, and January 18, 2025. Patients who were not suitable for CT scan evaluation were excluded.

CT scans were carried out with multi-slice CT scanner systems (GE Revolution EVO, GE Medical Systems, Milwaukee, WI, USA). Images were acquired from the vertex to the base of the skull in helical mode (kVp 120, mAs 250) and reconstructed in the axial plane with 0.625 mm thickness.

For patients who presented to the ED due to orbital injuries and underwent CT scanning, data were recorded on age, gender, type of trauma, the presence of additional trauma locations (if any), the injured eye, the cause of injury, and the specific location of the injury.

Statistical Analysis

For continuous variables (e.g., age), descriptive statistics were calculated and reported as the mean±standard deviation, median, minimum, and maximum values. Discrete variables were summarized using frequency counts and percentages. The Kolmogorov–Smirnov test was employed to evaluate the normality of continuous data distributions. Comparisons of age across different trauma aetiologies were conducted using the Kruskal–Wallis variance analysis. For variables exhibiting statistically significant differences on the Kruskal–Wallis test, subsequent group-wise disparities were delineated via a Kruskal–Wallis multiple comparisons test. Furthermore, intergroup comparisons of age across trauma types were performed using the Mann–Whitney U test. The Chi-square test was applied for the comparative analysis of nominal variables presented in contingency tables. All statistical analyses were executed using IBM SPSS Statistics version 20 (Chicago, IL, USA), with a p-value of <0.05 considered indicative of statistical significance.

RESULTS

A total of 314 patients were included in the study. The cohort displayed a mean age of 46.54±18.23 years, with ages ranging from 18 to 79 years. Males comprised 69.1% (n=217) of the sample population. Blunt trauma was identified in 64.3% (n=202) of cases, whereas road traffic accidents were responsible for injuries in 32.5% (n=102) of patients. Additionally, 55.1% (n=173) of the patients sustained injuries to the right eye (Table 1).

Table 1. Patient demographic and epidemiologic variables and their categories

	n	%
Gender		
Female	97	30.9
Male	217	69.1
Trauma type		
Blunt	202	64.3
Penetrating	112	35.7
Concomitant trauma		
Absent	271	86.3
Present	43	13.7
Injured eye		
Right	173	55.1
Left	124	39.5
Bilateral	17	5.4
Trauma mechanism		
Road traffic accident	102	32.5
Occupational injury	23	7.3
Gunshot injury	90	28.7
Fall from height	21	6.7
Fall from ground	64	20.4
Violence	14	4.5

In the distribution of injury localizations among patients, osseous injuries were identified in 202 cases (64.3%), with the orbital floor being the most commonly affected site, noted in 79 patients (39.1%) (Table 2).

Frequency and percentage values represent the proportion of patients relative to the total sample size. Some patients sustained multiple traumas, resulting in a total number of injuries that exceeds the number of patients.

Patients presenting with blunt trauma were significantly older ($p<0.001$). Furthermore, individuals who sustained injuries from falls from height or falls from the ground exhibited significantly higher ages compared to those with other injury mechanisms ($p<0.001$ for both comparisons). Additionally,

Table 2. Distribution of injury localizations among patients

	n	%
Bone		
Absent	112	35.7
Present	202	64.3
Bone type (n=202)		
Floor	79	39.1
Medial wall	51	25.2
Roof	40	19.8
Mix	23	11.4
Lateral wall	9	4.5
Anterior chamber		
Absent	203	64.6
Present	111	35.4
Globe		
Absent	239	76.1
Present	75	23.9
Intraconal orbit		
Absent	268	85.4
Present	46	14.6
Optic nerve		
Absent	296	94.3
Present	18	5.7
Extraocular muscles/ extraconal orbit		
Absent	292	93.0
Present	22	7.0

Due to some patients having multiple injuries, the total number of traumas was higher than the number of patients. Frequency and percentage values show the ratio of patients and the total number of patients.*

patients with road traffic accidents demonstrated a higher mean age relative to those who experienced gunshot injuries (p<0.05) (Table 3).

Table 3. Comparison of patient ages across trauma types and aetiologies

	Age		
	Mean±SD	Median (min- max)	p value
Trauma type			
Blunt	52.53±17.77	61 (18-79)	<0.001[b]
Penetrating	35.75±13.51	31 (18-66)	
Trauma mechanism			
Road traffic accident	45.15±18.36	47.5 (18-75)	<0.001[d]
Occupational injury	34.83±7.64	33 (24-48)	
Gunshot injury	35.81±14.26	31 (18-66)	
Fall from height	64.76±3.63	65 (60-77)	
Fall from ground	65.94±4.14	66 (59-79)	
Violence	29.00±3.65	28 (22-38)	

b: Mann-Whitney U test, d: Kruskal-Wallis variance analysis, SD: Standard deviation

Among female patients, the incidence of road traffic accidents and falls from the ground were significantly elevated, whereas male patients were more frequently affected by gunshot injuries (p<0.001 for all comparisons) (Table 4).

Table 4. Comparative analysis of trauma types and mechanisms according to gender

	Female		Male		
	n	%	n	%	p value
Trauma type					
Blunt	83	85.6	119	54.8	<0.001[c]
Penetrating	14	14.4	98	45.2	
Trauma mechanism					
Road traffic accident	48	49.5	54	24.9	<0.001[c]
Occupational injury	0	0	23	10.6	
Gunshot injury	14	14.4	76	35.0	
Fall from height	5	5.2	16	7.4	
Fall from ground	28	28.9	36	16.6	
Violence	2	2.1	12	5.5	

c: Chi-Square test /Fisher's Exact test

Anterior chamber injuries were significantly more widespread among male patients (p<0.001), while female patients exhibited a higher frequency of injuries involving osseous structures, the globe, the intraconal orbital space, the optic nerve, muscular tissues, and extraocular muscles within the extraconal orbital space (with corresponding p-values of p<0.001, p=0.05, p<0.01, p<0.01, p<0.01, and p<0.05, respectively) (Table 5, Figure 1 a,b,c,d,e,f).

Table 5. Comparative analysis of orbital injury findings between female and male patients

	Female		Male		p value
	n	%	n	%	
Bone	83	85.6	119	54.8	<0.001[c]
Anterior chamber	12	12.4	99	45.6	<0.001[c]
Globe	30	30.9	45	20.7	0.050[c]
İntraconal orbit	22	22.7	24	11.1	0.007[c]
Optik nerve	11	11.3	7	3.2	0.004[c]
Extraocular muscles/ extraconal orbit	12	12.4	10	4.6	0.013[c]

c: Chi-Square test

Traumatic brain injury was observed in 43 patients (13.7%) (Figure 2 a,b).

DISCUSSION

Orbital injury represents a critical medical issue due to its potential to inflict substantial and long-term damage on both the anatomical integrity and functional capacity of the eye and adjacent structures. The ED serves as the primary setting for the initial evaluation, diagnosis, and acute management

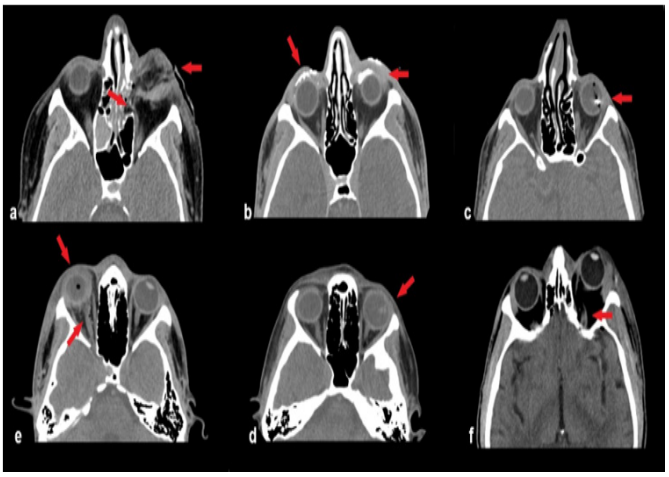

Figure 1. In the axial computed tomography examinations, a disorganized globe, left extraconal and intraconal heterogeneous density and millimetric air values were observed. Left medial rectus muscle is not observed (**a**), foreign body intensities are observed in bilateral preseptal areas (**b**), the millimetric metallic foreign body is observed in the left globe (**c**), deformation, haemorrhagic intensities, and millimetric air density are observed in the right globe. Loss of integrity and millimetric air densities are observed in the right optic nerve (**e**), the lens is not observed on the left, but it is observed in the vitreous fluid (**d**), and loss of integrity is observed in the left optic nerve (**f**) (red arrows to all)

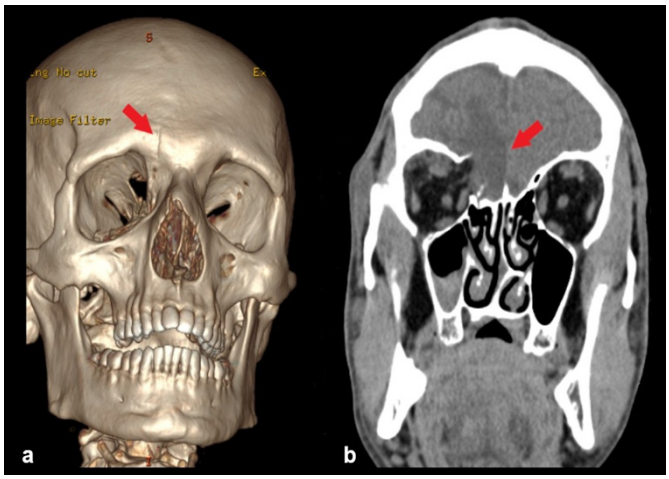

Figure 2. In the 3D computed tomography scan, fracture lines are observed in the medial orbital wall on the right (**a**), and in the coronal section, densities consistent with oedema and haemorrhage are observed in the right frontal brain parenchyma at this level (**b**) (red arrows)

of such injuries. CT remains the imaging modality of choice, given its advanced sensitivity in identifying orbital fractures, associated soft tissue damage and foreign bodies.

The financial burden associated with orbital injury has increased considerably over time, with ED expenditures rising substantially, highlighting the necessity for targeted preventive measures to reduce healthcare costs and enhance clinical outcomes. Epidemiological data indicate a marked increase in the incidence of orbital injuries, particularly blunt trauma, over the study period, with cases rising from 61.3 per million person-years in 2013 to 133.0 per million person-years in 2022.[5]

Blunt orbital trauma is recognized as a predominant contributor to ocular injuries, with its aetiology demonstrating considerable variation across diverse populations. Individuals from lower socioeconomic strata appear to be at a higher risk, likely due to increased exposure to environments where the incidence of violence and accidents is higher.[6]

Motor vehicle accidents are frequently implicated as a principal cause of blunt orbital trauma, a phenomenon that is particularly pronounced in urban areas characterized by high traffic density.[7] Within the spectrum of trauma mechanisms, falls and assaults have been most commonly reported. In a prospective investigation, al-Qurainy et al.[8] documented those assaults accounted for 49.9% of cases, whereas falls and motor vehicle accidents comprised 19% and 12.4% of incidents, respectively—a pattern corroborated by a more recent study by Chow et al.[9], which reported figures of 48%, 17%, and 21% for assault, falls, and motor vehicle accidents, respectively.[8,9] Conversely, Amrith et al.[10] identified motor vehicle accidents as the largest proportion of cases at 36.5%, with assaults representing 12.5%. Furthermore, another study observed blunt trauma as the contributing factor in 48.3% of cases, with falls and motor vehicle accidents accounting for 24.3% and 25.4% of cases, respectively.[11]

In this study, blunt trauma emerged as the most frequently observed injury, with motor vehicle accidents representing the main etiological factor. Given the variability observed among studies with adequate sample sizes, these inconsistencies are likely due to regional and cultural influences.[11]

Young adults, particularly males aged 20–29, demonstrate an elevated exposure to ocular injuries, a phenomenon largely attributable to their dynamic lifestyles and active participation in sports and physical activities. This cohort is predisposed to sustaining injuries from blunt impacts, with a considerable number of cases occurring in domestic and commercial environments. Additionally, the incidence of ocular injury in this demographic is further exacerbated by occupational hazards, especially within industrial settings where the use of protective eyewear remains insufficient.[12]

In contrast, the elderly population experiences the highest incidence of orbital trauma, primarily as a consequence of falls, which represent the major reason of injury in this age group. In this study, similarly, the frequency of falls was significantly higher among older individuals compared to other age cohorts. Implementation of comprehensive fall prevention strategies and the integration of safety-enhancing features in residential design may be fundamental in reducing the rising rates of orbital trauma in the elderly.[5]

Moreover, the results revealed that road traffic accidents and ground-level falls were more prevalent among female patients, whereas gunshot injuries were more frequently encountered in male patients. Epidemiological studies display consistent male predominance in orbital trauma cases. For instance, a study conducted at a London trauma centre documented that 82% of patients with orbital fractures were male.[12] Furthermore, a retrospective review at Ahmadu Bello University Teaching Hospital identified 142 patients with orbital/ocular trauma over a two-year period, yielding a male-to-female ratio of 3:1, thereby highlighting the higher incidence of these injuries in males.[13]

Within the geriatric cohort, our findings indicated a higher prevalence of females compared to males, whereas males

predominated in all other age groups. This observation is consistent with prior research, which has documented an increased susceptibility among elderly females to falls and maxillofacial trauma—a trend that may be partly explained by the significant female representation within this population.[14]

Moreover, males are excessively represented in high-risk occupational sectors such as construction, metalworking, and agriculture, which are inherently associated with an elevated incidence of ocular injuries. These professions frequently involve exposure to hazards including airborne debris, chemical agents, and heavy machinery, thereby amplifying the risk of ocular injury. Additionally, tendency among men to underestimate the risks inherent in their work environments often results in diminished compliance with established safety protocols.

Men display a higher susceptibility to orbital injury than women due to a complex interplay of biological, sociocultural, and environmental factors. The elevated incidence of orbital injuries in men is largely a consequence of increased exposure to risk determinants, such as interpersonal violence and occupational hazards. In particular, males living in socioeconomically disadvantaged areas face an increased risk of assault-related orbital injury. Socioeconomic variables—including poverty, unemployment, and lower educational attainment—are associated with higher injury rates, as these factors frequently correspond with increased crime and violence, thereby contributing to the gender difference observed in orbital trauma incidence.[15,16]

Orbital injury in the adult population remains a critical clinical issue due to its potential to result in severe ocular and facial injuries. Multislice CT combined with three-dimensional reconstructions has proven effective in accurately assessing the extent of orbital fractures and identifying associated complications.

Orbital trauma resulting in osseous fractures constitutes a significant concern in maxillofacial injuries, frequently arising from direct impacts to the periorbital region or the adjacent facial bones. Such fractures can lead to both functional deficits and cosmetic deformities. In the study conducted by Goelz et al.[17], the orbital floor was involved in 165 patients (66.8%), establishing it as the most widespread fracture position. Conversely, another study identified the lateral orbital wall as the most commonly fractured region, with 105 patients (71.43%) sustaining fractures in this area, while the orbital floor ranked as the second most frequent site, affecting 55 patients (37.42%).[18] In this study, osseous fractures were most frequently observed in the lateral orbital wall, followed by the orbital floor. Although the lateral wall is the most rigid among the orbital walls, its distinct anatomical position renders it particularly susceptible to direct traumatic impacts, especially in cases of midfacial trauma resulting from road traffic accidents and falls.[18] In the study cohort, road traffic accidents, and falls were identified as the principal etiological factors for trauma.

In this study, anterior chamber injuries were significantly more frequent among male patients. Previous investigations have demonstrated that blunt ocular trauma—which often involves the anterior chamber—mainly affects men, with 82% of reported cases occurring in this population.[19] This high incidence among males can be attributed to their heightened exposure to high-risk activities and environments, including certain occupational settings and sports.

Optic nerve injury may occur via both direct and indirect mechanisms. Direct trauma arises when the optic nerve is physically compromised by penetrating injuries, such as those induced by foreign bodies or osseous fragments, leading to shearing forces or the formation of a hematoma within the nerve.[20,21]

Indirect injuries to the optic nerve arise from force, typically due to blunt trauma, which can lead to deformation of the optic canal and subsequent damage to the nerve. This mechanism, termed indirect traumatic optic neuropathy, occurs as forces transmit through the skull and adversely affect the optic nerve.[21,22] In this study, optic nerve injury was the least frequently observed among the evaluated injuries.

Additionally, traumatic brain injury was present in 13.7% of patients. The coexistence of polytrauma, including traumatic brain injuries, often complicates the management of orbital injuries, underscoring the necessity for a coordinated, multidisciplinary approach. Such brain injuries can exacerbate the clinical consequences of orbital trauma, increasing the risk of neurological deficits and subsequent infections.[23]

Limitations

Several limitations of this study must be acknowledged. The retrospective, single-centre design restricts the generalizability of our findings, and the exclusion of patients with minor injuries who did not undergo CT imaging may introduce selection bias, potentially expanding the apparent occurrence and severity of orbital injury. Future research should focus on prospective, multicentre studies with broader inclusion criteria to validate these observations and to further elucidate the epidemiological and clinical nuances of orbital injuries, thereby informing more effective clinical interventions and preventive measures.

CONCLUSION

In conclusion, orbital injury represents a critical and multifaceted clinical challenge in the ED, with significant implications for both ocular function and facial integrity. Our study, which encompassed a diverse patient cohort, demonstrates that the incidence, type, and aetiology of orbital injuries vary markedly with age and gender. Blunt trauma emerged as the predominant mechanism, particularly in older populations and in association with falls, whereas high-risk activities and occupational exposures contributed substantially to the burden of injuries observed in younger male patients. Additionally, the frequent occurrence of concomitant injuries, including traumatic brain injury, underscores the complexity of managing these patients and highlights the necessity for a coordinated, multidisciplinary approach.

ETHICAL DECLARATIONS

Ethics Committee Approval

The approval was granted by the Ministry of Health Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 29.01.2025, Decision No: 2025/0185).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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The prognostic role of the CHA_2DS_2-VASc score in patients with acute myocardial infarction receiving extracorporeal membrane oxygenation following out-of-hospital cardiac arrest

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ABSTRACT

Aims: The CHA_2DS_2-VASc scoring system has been widely used for stroke risk stratification in patients with atrial fibrillation, yet evidence regarding its prognostic value in other critical settings remains limited. This study aimed to assess the utility of the CHA_2DS_2-VASc score in predicting mortality in patients with acute myocardial infarction (AMI) who received veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support following out-of-hospital cardiac arrest.

Methods: This retrospective study included 41 patients with AMI requiring VA-ECMO after OHCA. Baseline demographics, clinical characteristics, and prognostic scores, including CHA_2DS_2-VASc, SAVE (Survival After Veno-Arterial ECMO), Glasgow Coma Scale (GCS), and acute physiology and chronic health evaluation (APACHE) II were recorded. Patients were categorized into three risk groups based on the CHA_2DS_2-VASc score: low (0 points), moderate (1 point), and high (≥2 points). According to the SAVE score, patients were classified into five risk groups: class I (≥5 points), class II (1–4 points), class III (−4 to 0 points), class IV (−9 to −5 points), and class V (≤−10 points). The primary outcome was in-hospital mortality.

Results: The overall in-hospital mortality rate was 58.5%. Patients with high risk group had a significantly higher mortality risk (HR: 3.12, 95% CI: 1.28-7.63, p=0.008). The SAVE score had the highest diagnostic performance, with a sensitivity of 81.2% and specificity of 76.5% (AUC=0.80). CHA_2DS_2-VASc (AUC=0.74) and APACHE II (AUC=0.72) also demonstrated good predictive performance. While CHA_2DS_2-VASc maintained a balanced sensitivity (70.8%) and specificity (64.7%), APACHE II had higher sensitivity (75.7%) but lower specificity (58.8%). GCS demonstrated the lowest diagnostic performance (AUC=0.68).

Conclusion: While the SAVE score, a risk model specifically designed for VA-ECMO, provides a strong prognostic evaluation, the CHA_2DS_2-VASc score could be a simple and easily applicable tool for early risk stratification in this high-risk population.

Keywords: CHA2DS2-VASc score, extracorporeal membrane oxygenation, cardiogenic shock, mortality

INTRODUCTION

Out-of-hospital sudden cardiac arrests (OHCA) continue to be a significant clinical issue, with acute coronary syndromes being the most prevalent etiological factor, especially in patients above 35 years of age.[1] Rapid and effective intervention is crucial in cardiac arrest. Although standard cardiopulmonary resuscitation (CPR) approaches can effectively reestablish circulation in numerous cases, they may be insufficient in ensuring optimal tissue perfusion and oxygenation for patients with refractory cardiac arrest.[2] In these complex scenarios, extracorporeal membrane oxygenation (ECMO) has been proposed as a promising rescue option. Specifically, veno-arterial ECMO (VA-ECMO) serves as a temporary cardiopulmonary support system by performing the heart's pumping function and the lungs' oxygenation, thereby preserving organ perfusion and increasing survival likelihood.[3,4]

The application of ECMO requires substantial resources and is an invasive procedure, with varying success rates among patients.[5-7] Hence, forecasting the prognosis of patients receiving ECMO therapy is crucial for avoiding unnecessary aggressive treatments and optimizing resource utilization. At this stage, various scoring systems have been developed as potential tools for predicting survival. One such scoring system is the SAVE (survival after veno-arterial ECMO) score, designed to predict survival in patients receiving VA-ECMO for refractory cardiogenic shock. This model assesses key clinical variables, including age, weight, underlying cardiac diagnosis, pre-ECMO organ dysfunction (such as

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renal or hepatic impairment), duration of intubation before ECMO initiation, and various vital signs or hemodynamic parameters.[8] Other scoring systems include the ENCOURAGE mortality risk score, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS) II, and Acute Physiology and Chronic Health Evaluation (APACHE) II.[9-11] However, their diagnostic performance differs between studies and continues to be an important area of investigation.[8-11]

The CHA_2DS_2-VASc score is designed to evaluate stroke risk in patients with atrial fibrillation and incorporates key cardiovascular risk factors, including congestive heart failure (CHF), hypertension, age (≥75 and 65–74), diabetes, previous stroke/transient ischaemic attack (TIA), vascular disease, and female sex.[12] Thus, it functions as a practical tool that indicates a patient's chronic comorbidity load. Additionally, its prognostic value has been validated in several studies conducted on populations beyond atrial fibrillation.[13-15] However, its effectiveness in predicting survival outcomes in patients undergoing ECMO therapy after cardiac arrest remains unexplored.

Considering that the SAVE and CHA_2DS_2-VASc scoring systems incorporate essential cardiovascular risk factors, we assumed that the CHA_2DS_2-VASc score might function as a useful prognostic tool for estimating survival outcomes in patients undergoing ECMO therapy after cardiac arrest. Therefore, this study aimed to compare the prognostic value of the VA-ECMO score and CHA_2DS_2-VASc score in predicting survival outcomes in patients with acute myocardial infarction (AMI) undergoing ECMO therapy following OHCA.

METHODS

This retrospective study was conducted on OHCA patients who underwent ECMO therapy at the coronary and cardiovascular surgery intensive care unit (ICU) of Lokman Hekim University Health Practice and Research Center between January 2020 and December 2024. The study was approved by the Lokman Hekim University Non-interventional Clinical Researches Ethics Committee (Date: 30.12.2024, Decision No: 2024/13) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). The need for informed consent was waived under the approval of the local ethics committee due to the retrospective design.

During the study period, a total of 2054 who admitted to the emergency department due to OHCA were retrospectively evaluated. Exclusion criteria included patients under 18 years old, those with chronic obstructive pulmonary disease, those with myocarditis, those with previous ECMO treatment, those with refractory VT/VF, those with heart or lung transplantation, those with malignancy or terminal organ failure, those diagnosed with severe neurological impairment or brain death, cases of profound pre-resuscitation hypothermia (<28°C), pregnant women, and patients with incomplete medical records. Following the exclusion criteria, a total of 42 patients were included in the final analysis.

Data Collection and Definitions

The hospital's electronic information system and patient files were used to gather demographic and clinical data. Pre-existing severe neurological disease or injury, malignancy, or other comorbidities with an extremely short expected survival, along with severe peripheral vascular disease, were regarded as contraindications for ECMO.[16,17] CHF was defined as recently decompensated heart failure, independent of left ventricular ejection fraction (LVEF) or the detection of moderate-to-severe left ventricular systolic dysfunction on cardiac imaging, even in asymptomatic cases.[18] Hypertension was defined as prior use of antihypertensive medications or a systolic/diastolic blood pressure of ≥140/90 mm Hg. Diabetes mellitus was defined as prior insulin or antidiabetic drug use or a fasting glucose level of ≥126 mg/dl. Transient ischemic attack (TIA) and systemic embolism were considered equivalent risk factors for stroke.[19] A history of myocardial infarction, peripheral arterial disease, or complex aortic plaques was considered indicative of vascular disease. Chronic renal failure (CRF) was defined as the presence of kidney damage or a glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 for at least 3 months. Acute renal failure (ARF) was defined as a creatinine level exceeding 1.5 mg/dl, regardless of the need for renal replacement therapy. Acute liver failure (ALF) was defined as total bilirubin ≥33 µmol/L or ALT/AST levels >70 U/L at the initiation of ECMO. The definition of acute central nervous system dysfunction (CNS) dysfunction included neurotrauma, stroke, encephalopathy (confusion or impaired consciousness), cerebral embolism, seizures, and epileptic syndromes.[20]

In the CHA_2DS_2-VASc scoring system, 1 point was assigned for CHF, hypertension, diabetes mellitus, age 65–74 years, female sex, and vascular disease, while 2 points were given for age ≥75 years and a prior stroke/TAI.[12] Patients were categorized into two groups according to their admission CHA_2DS_2-VASc score: the low risk group (CHA_2DS_2-VASc score 0), moderate risk group (CHA_2DS_2-VASc score), and the high risk group (CHA_2DS_2-VASc ≥ 2).[21]

The SAVE score was assessed using previously established factors, including age, weight, pre-existing cardiac disease, organ dysfunction before ECMO (such as renal or hepatic impairment), intubation duration before ECMO initiation, and various hemodynamic or vital parameters.[8] Based on the SAVE score, patients are classified into five risk groups: class I risk (≥5 points), class II (1–4 points), class III (−4 to 0 points), class IV (−9 to −5 points), and class V (≤−10 points). Higher SAVE scores indicate better survival chances, while lower scores correlate with increased mortality risk.[8]

ECMO Procedure

At our institution, ECMO initiation and weaning protocols align with widely accepted clinical strategies. Peripheral VA-ECMO cannulation was performed in the ICU using the percutaneous Seldinger technique via the femoral vessels. To prevent thromboembolic complications during ECMO support, unfractionated heparin infusion was administered, targeting an activated clotting time (ACT) of 180–200 seconds and an activated partial thromboplastin time (aPTT) of 60–80 seconds. The ECMO pump flow rate was adjusted

to maintain adequate perfusion and hemodynamic stability, with additional support provided as needed through fluid resuscitation, blood products, inotropes, or vasopressors. Neurological function was regularly assessed using the Glasgow Coma Scale (GCS), including evaluations of consciousness, motor responses, and sensory function. For sedated patients, daily sedation interruptions were performed to facilitate neurological assessment. ECMO weaning was considered once the patient achieved hemodynamic stability, either with minimal pharmacological support or independently. The patient's circulatory status was evaluated at an ECMO flow rate of 1 L/min, and ECMO support was discontinued if sufficient perfusion was maintained without mechanical assistance.

Statistical Analysis

All data were analyzed with STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation values, while non-normally distributed variables are given as median (25^{th}-75^{th} quartiles) values. Student T test or Mann-Whitney U test were used for comparisons between two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher-exact tests. Mortality was evaluated using Cox regression analysis, and the results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). ROC curve analysis was used to assess diagnostic performance, with threshold values determined via the Youden index method. AUC curves were compared using a nonparametric approach, employing the generalized U-statistics method to estimate the covariance matrix, as previously described by DeLong et al.[22] Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULTS

A total of 41 patients were included in the study, with a mean age of 54.5±11.7 years, and the majority being female (58.5%). Among the patients, 51.2% were smokers, while 31.7% had hypertension, 53.7% had diabetes mellitus, 70.7% had coronary artery disease (CAD), 24.4% had chronic heart failure (CHF), 9.8% had a history of stroke, and 29.3% had chronic kidney disease (CKD). The median CHA_2DS_2-VASc score was 2, and 56.1% of the patients were classified as high-risk according to this scoring system. All patients underwent percutaneous coronary intervention (PCI), with the most common AMI location being the anterior wall. Intra-aortic balloon pump (IABP) support was used in 51.2% of the patients. The median duration of ECMO support was 6.5 days (IQR: 2–9 days), while the median total hospital stay was 16 days (IQR: 16–25 days). The in-hospital mortality rate was 58.5%.

The demographic characteristics of the patients are presented in Table 1 in detail. Demographic variables significantly associated with mortality included older age (HR: 1.04, 95% CI: 1.0–1.08, p=0.039), hypertension (HR: 3.10, 95% CI: 1.25–7.69, p=0.018), diabetes mellitus (HR: 2.38, 95% CI: 1.02–5.76, p=0.048), and CAD (HR: 3.16, 95% CI: 1.05-9.49, p=0.040). The other demographic variables were not associated with mortality (Table 1).

The pre-ECMO clinical findings of the patients are presented in detail in Table 2. Patients with ARF had a higher risk of mortality. However, no significant association was found between mortality and other clinical findings (Table 2).

The prognostic scoring systems and clinical severity scores of the patients are presented in Table 3. The CHA_2DS_2-VASc score was significantly higher in the non-survivor group compared to the survivor group (3.0 vs. 1.5, p<0.001) (Figure 1). Patients classified as high risk based on the CHA_2DS_2-VASc score had a significantly higher mortality risk (HR: 3.12, 95% CI: 1.28-7.63, p=0.008). Similarly, the SAVE score was significantly lower in non-survivors than in survivors (-12.0 vs. -5.0, p=0.002) (Figure 1). Risk stratification based on SAVE score classes demonstrated a significant association with mortality. Compared to class III (reference group), patients in class IV had a higher mortality risk (HR: 3.11, 95% CI: 1.10–10.22, p=0.039), while those in class V had an even greater mortality risk (HR: 7.30, 95% CI: 2.16-24.66, p=0.001). Regarding clinical severity scores, lower GCS scores (HR: 0.75, 95% CI: 0.58–0.96, p=0.031) and higher APACHE II scores (HR: 1.07, 95% CI: 1.01–1.13, p=0.026) were significantly associated with increased mortality (Table 3).

To prevent multicollinearity, age, hypertension, and diabetes mellitus, which are core components of the CHA_2DS_2-VASc score, were not included as separate variables in the multivariable model. Furthermore, the variance inflation factor (VIF) between CAD and the CHA_2DS_2-VASc score was high (VIF=11.6), indicating a strong collinearity between these variables. For this reason, CAD was omitted from the multivariable regression analysis. Additionally, components of the SAVE and APACHE II scores were excluded from the regression model due to high collinearity. The multivariable regression model showed that the high-risk group based on the CHA_2DS_2-VASc score and class IV and V classifications based on the SAVE score were independent predictors of mortality (Table 4). The survival rate was 48% in the moderate-risk group and 23% in the high-risk group. On the other hand, the survival rate was 52% in class III, 31% in class IV, and 16% in class V (Figure 2, Table 4).

Among the assessed prognostic risk scoring systems, the SAVE score exhibited the highest predictive accuracy, with an AUC of 0.80 (95% CI: 0.64–0.91), indicating a strong discriminatory ability. Furthermore, it demonstrated the highest sensitivity (81.2%) and specificity (76.5%), suggesting its superior capacity to identify high-risk patients while minimizing false-positive classifications. The CHA_2DS_2-VASc score (AUC=0.74, 95% CI: 0.57–0.86) and APACHE II score (AUC=0.72, 95% CI: 0.56–0.86) also exhibited good predictive performance. While CHA_2DS_2-VASc maintained a relatively balanced sensitivity (70.8%) and specificity (64.7%), APACHE II demonstrated a higher sensitivity (75.7%) but lower specificity (58.8%), indicating a greater likelihood of detecting high-risk patients at the cost of increased false-positive rates. The GCS had the lowest predictive performance among the evaluated scores, with an AUC of 0.68 (95% CI: 0.53–0.83) (Table 5).

Table 1. Demographic characteristics of the study population

Variables	All population n=41	Survival		Univariable regression		
		Survived n=17	Died n=24	HR	95% CI	p
Age, years	54.5±11.7	54.1±10.2	54.8±12.8	1.04	1-1.08	0.039*
Female, n (%)	24 (58.5)	10 (58.8)	14 (58.3)	0.66	0.28-1.54	0.335
Weight, kg	76.0±18.0	77.1±19.6	75.2±17.2	0.99	0.97-1.01	0.323
BMI, kg/m²	25.4±5.2	26.3±5.3	24.8±5.2	0.97	0.89-1.05	0.399
Smoking, n (%)	21 (51.2)	9 (52.9)	12 (50.0)	0.55	0.23-1.28	0.162
Comorbidity, n (%)						
Hypertension	13 (31.7)	4 (23.5)	9 (37.5)	3.10	1.25-7.69	0.015*
Diabetes mellitus	13 (31.7)	5 (29.4)	8 (33.3)	2.38	1.02-5.76	0.048*
CAD	29 (70.7)	11 (64.7)	18 (75.0)	3.16	1.05-9.49	0.040*
CHF	10 (24.4)	4 (23.5)	6 (25.0)	1.27	0.49-3.24	0.622
Stroke	4 (9.8)	1 (5.9)	3 (12.5)	2.51	0.74-8.53	0.142
CRF	12 (29.3)	6 (35.3)	6 (25.0)	0.97	0.38-2.49	0.956
CPR duration, minutes	46.1±11.6	46.8±7.3	45.6±14.1	0.99	0.96-1.03	0.648
AMI location, n (%)						
Anterior	26 (63.4)	11 (64.7)	15 (62.5)	ref		
Inferior	11 (26.8)	3 (17.6)	8 (33.3)	1.52	0.65-3.57	0.333
Other	4 (9.8)	3 (17.6)	1 (4.2)	0.21	0.03-1.54	0.123
IABP, n (%)	21 (51.2)	9 (52.9)	12 (50.0)	0.79	0.35-1.78	0.567

The data are expressed as the mean±SD, median (IQR), or frequency (%). * indicates statistical significance at p<0.05. AMI: Acute myocardial infarction, BMI: Body-mass index, CAD: Coronary artery disease, CHF: Chronic heart failure, CI: Confidence interval, CPR: Cardiopulmonary resuscitation; CRF: Chronic renal failure, HR: Hazard ratio, IABP: Intra-aortic balloon pump, ref: Reference category

Table 2. Pre-extracorporeal membrane oxygenation clinical findings of the study population

Variables	All population n=41	Survival		Univariable regression		
		Survived n=17	Died n=24	HR	95% CI	p
Intubation, h	10.0 (7.0-16.0)	9.0 (6.0-14.0)	11.0 (7.0-16.0)	1.02	0.92-1.09	0.126
DBP > 40 mm Hg	8 (19.5)	5 (29.4)	3 (12.5)	0.48	0.14-1.63	0.242
PP ≤ 20 mm Hg	26 (63.4)	9 (52.9)	17 (70.8)	2.16	0.88-5.31	0.095
Ejection fraction, %,	29.8±6.1	29.1±7.1	30.2±5.4	1.04	0.97-1.1	0.250
sPAP, mmHg	34.3±5.8	35.6±6.1	33.3±5.5	0.95	0.87-1.04	0.251
Laboratory findings						
Hemoglobin, g/dl	12.3±1.8	12.2±2.1	12.3±1.5	1.06	0.85-1.32	0.621
WBC, 10^3/uL	8.6±2.9	8.0±3.2	9.0±2.6	1.05	0.93-1.19	0.433
LDL, mg/dl	120.6±28.9	116.9±31.4	123.3±27.4	1.01	0.99-1.02	0.240
Triglyceride, mg/dl	156.6±81.5	147.9±73.1	162.7±87.9	1.00	0.98-1.01	0.493
TT, mmol/L	24.1±10.3	25.3±9.5	23.3±11.0	0.98	0.94-1.02	0.267
ALT, UI/L	134.2±99.9	113.5±108.1	148.9±93.3	1.00	0.98-1.01	0.185
AST, UI/L	226.0±150.6	226.5±139.8	225.7±160.8	1.00	0.98-1.01	0.890
Creatinine, mg/dl	1.8±0.4	1.8±0.5	1.8±0.4	0.96	0.39-2.33	0.924
UREA	39.0 (26.0-64.0)	39.0 (25.0-58.0)	43.0 (27.5-75.0)	1.01	0.97-1.02	0.219
CRP, mg/L	10.1 (4.7-35.0)	9.3 (4.7-35.0)	14.1 (8.1-35.0)	1.00	0.98-1.01	0.609
Albumin, g/dl	3.7 (3.4-3.9)	3.9 (3.4-3.9)	3.6 (3.4-3.9)	0.98	0.91-1.06	0.597
HCO, mmol/L	17.5±3.2	17.6±2.8	17.4±3.4	1.01	0.88-1.17	0.857
Acute organ failures						
Renal failure	24 (58.5)	7 (41.2)	17 (70.8)	2.28	1.02-5.34	0.044*
Liver failure	28 (68.3)	9 (52.9)	19 (79.2)	2.20	0.81-5.95	0.122
CNS dysfunction	8 (19.5)	2 (11.8)	6 (25.0)	1.16	0.46-2.93	0.754
ECMO duration, days	6.5 (2-9)	7 (2-10)	5 (2-8)	0.92	0.68-1.23	0.106
Hospital duration, days	16 (10-25)	25 (17-30)	13 (8-15)	-	-	-

The data are expressed as the mean±SD, median (IQR), or frequency (%). * indicates statistical significance at p<0.05. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CI: Confidence interval, CNS: Central nervous system, CRP: C-reactive protein, DBP: Diastolic blood pressure, ECMO: Extracorporeal membrane oxygenation, HCO: Bicarbonate, HR: Hazard ratio, LDL: Low-density lipoprotein, PP: Pulse pressure, sPAP: Systolic pulmonary artery pressure, TT: Total bilirubin, WBC: White blood cell count

Table 3. Association of prognostic scores and clinical severity indices with mortality

Variables	Survival		Univariable regression		
	Survived n=17	Died n=24	HR	95% CI	p
CHA_2DS_2-VASc	1.5 (1.0-3.0)	3.0 (1.5-4.0)	1.58	1.26-1.99	<0.001*
Moderate risk, n (%)	11 (64.7)	7 (29.2)	ref		
High risk, n (%)	6 (35.3)	17 (70.8)	3.12	1.28-7.63	0.008*
SAVE score	-5.0 [(-9.0)-(-3.0)]	-12.0 [(-17.0)-(-8.0)]	0.89	0.83-0.96	0.002*
Risk class, n (%)					
III	9 (52.9)	4 (16.7)	ref		
IV	5 (29.4)	9 (37.5)	3.11	1.10-10.22	0.039*
V	3 (19.6)	11 (45.8)	7.30	2.16-24.66	0.001*
GCS	7.2±2.2	5.4±1.6	0.75	0.58-0.96	0.031*
APACHE II score	25.1±7.4	31.0±6.4	1.07	1.01-1.13	0.026*

The data are expressed as the mean±SD, median (IQR), or frequency (%). * indicates statistical significance at p<0.05. APACHE II: Acute physiology and chronic health evaluation II, CI: Confidence interval, GCS: Glasgow Coma Scale, HR: Hazard ratio, SAVE: Survival after veno-arterial ECMO

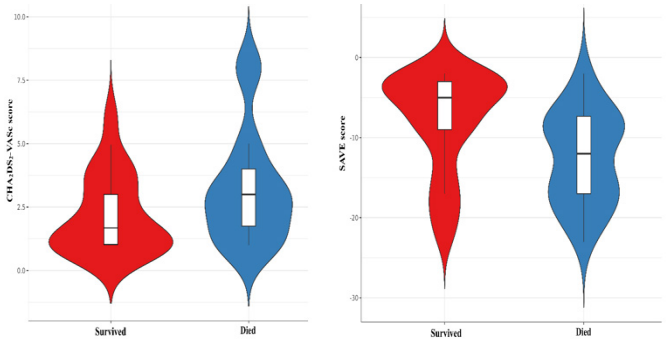

Figure 1. Comparison of CHA_2DS_2-VASc and SAVE scores between survived and died patients
SAVE: Survival after veno-arterial ECMO

Table 4. Independent predictor of mortality

Variables	Multivariable regression			Survival rate (%)
	HR	95% CI	p	
CHA_2DS_2-VASc				
Moderate risk, n (%)	ref			48.0
High risk, n (%)	2.72	1.29-6.49	0.045*	23.0
SAVE score				
Risk class, n (%)				
III	ref			52.0
IV	3.09	1.08-10.05	0.048*	31.0
V	5.57	1.57-19.82	0.008*	16.0
APACHE II score	1.03	0.97-1.09	0.231	-

The data are expressed as the mean±SD, median (IQR), or frequency (%). * indicates statistical significance at p<0.05. APACHE II: Acute physiology and chronic health evaluation II, GCS: Glasgow Coma Scale, HR: Hazard ratio, CI: Confidence interval, SAVE: Survival after veno-arterial ECMO

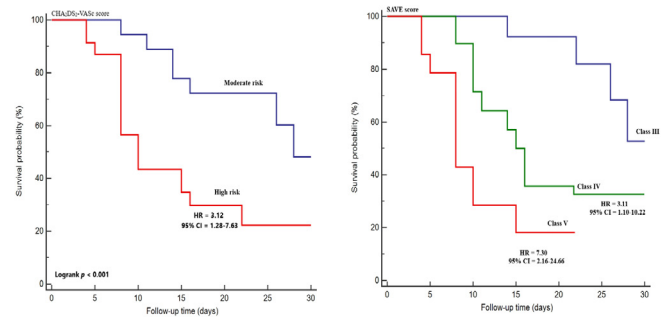

Figure 2. The survival rate according to CHA_2DS_2-VASc and SAVE score classifications

Table 5. Diagnostic performance of prognostic risk scores in predicting mortality

	AUC±SE	95%CI	Sens.	Spec.	Threshold
APACHE II	0.72 ± 0.08	0.56-0.86	75.7	58.8	>24
GCS	0.68 ± 0.08	0.53-0.83	73.7	57.5	≤6
CHA_2DS_2-VASc	0.74 ± 0.08	0.57-0.86	70.8	64.7	≥2
SAVE score	0.80 ± 0.07	0.64-0.91	81.2	76.5	<-6

APACHE II: Acute physiology and chronic health evaluation II, CI: Confidence interval, GCS: Glasgow Coma Scale; SAVE: Survival after veno-arterial ECMO, Sens: Sensitivity, Spec: Specificity

DISCUSSION

To the best of our knowledge, this is the first study to investigate the prognostic value of the CHA_2DS_2-VASc score in AMI patients undergoing ECMO following OHCA. Our findings indicate that CHA_2DS_2-VASc and other prognostic scores were significantly higher in non-survivors compared to survivors. Although the SAVE score demonstrated the highest diagnostic performance in predicting in-hospital mortality, the CHA_2DS_2-VASc score exhibited an acceptable predictive value. These findings suggest that the CHA_2DS_2-VASc score may serve as a feasible screening tool for pre-ECMO mortality risk assessment.

Studies conducted on OHCA patients have reported post-ECMO 30-day mortality rates varying between 43% and 76%.[23-26] In line with these studies, the survival rate observed in our study was 58.5%. Although general scoring systems such as APACHE II, SAPS II, and SOFA are widely used for mortality prediction in the heterogeneous population of ICUs, their limitations in patients undergoing ECMO have been reported.[8,11,27] A previous study reported that APACHE II scores demonstrated lower mortality rates compared to the SAVE score. In the same study, Bland-Altman analysis revealed a mean predicted mortality difference of 17.6% (95% CI: 7.6%–27.6%, p<0.0001) between the SAVE and APACHE II scores. Additionally, APACHE II was shown to underestimate mortality compared to SAVE up to an 80% mortality threshold, beyond which it provided higher mortality estimates.[28] This finding indicates that APACHE II might undervalue the potential benefits of ECMO in low-risk patients while overestimating disease severity in high-risk

patients. Our findings not only support but also extend the outcomes of these studies. In the present study, although ICU risk scores (APACHE II, GCS) and the ECMO-specific risk score (SAVE) were elevated in deceased patients, the SAVE score exhibited superior sensitivity and specificity.

The better diagnostic performance of the SAVE score over ICU-specific scoring systems may be due to several factors. Firstly, GCS and APACHE II were originally designed for the general ICU population without ECMO, meaning they may not fully capture the unique physiological status and risks of patients requiring VA-ECMO. In contrast, the SAVE score was developed specifically from VA-ECMO patient data, making it inherently more tailored to this population. Secondly, all of our patients experienced OHCA and underwent immediate PCI prior to ECMO initiation. Given that revascularization can partially restore cardiac function and improve hemodynamic stability, the physiological parameters incorporated into the APACHE II score at ICU admission may not fully reflect the initial severity of shock at the time of arrest. It has been emphasized that the APACHE II score may not accurately reflect the true severity of a patient's condition at the time of arrest, potentially leading to an underestimation of risk, especially in subgroups with lower mortality risk and rapidly correctable conditions.[28] Finally, patient profile differences may also contribute to variations in scoring system performance. In the cohort where the SAVE score was established, CHF (33%), AMI (29%), valvular heart disease (17%), and refractory VT/VF (13%) were the most common conditions,[8] whereas in our VA-ECMO series, all cases were AMI.

In fact, numerous studies on cardiac arrest patients have shown that patient profile can be an important prognostic indicator.[29-32] In a recent comprehensive analysis of more than 5.000 ECMO patients, advanced age was found to be a significant factor reducing survival probability. The survival rate for the 65–74 age group was 32% lower than that of the 18–49 age group, and for patients over 75, it was 46% lower.[33] Similarly, female sex or presence of comorbidities, such as diabetes mellitus, hypertension, CHF, has been found to be an independent predictor of mortality after ECMO.[31,34-36] These findings indicate that the risk factors encompassed in the CHA_2DS_2-VASc score, such as age and the burden of comorbidities, may play a crucial role in determining survival probability after ECMO. To our knowledge, this is the first study to report that an elevated CHA_2DS_2-VASc score is associated with higher post-ECMO mortality in OHCA patients. Based on the ROC curve analysis, a cutoff value of ≥2 was established for mortality risk, which corresponded with the general risk classification defined by the European Society of Cardiology (ESC) guidelines.[21] The CHA_2DS_2-VASc score exhibited sensitivity comparable to ICU risk scores. Although its specificity was limited, it remained higher than that of ICU risk scores. This aligns with the regression analysis results, where it was identified as an independent predictor. Furthermore, several studies conducted on cardiac arrest patients, have demonstrated the prognostic role of the CHA_2DS_2-VASc score.[14,37-41] The score's prognostic role is likely due to the cumulative pathophysiological effects of its components. Advanced age, hypertension, and diabetes, major components of the CHA_2DS_2-VASc score, are associated with progressive microvascular damage and decreased organ reserve, which can hinder recovery from global ischemic injury after cardiac arrest. Diabetes and hypertension impair cerebral and myocardial circulation, worsening ischemia-reperfusion injury and reducing the likelihood of full neurological recovery. Additionally, CHF and vascular disease indicate a limited cardiopulmonary reserve and widespread atherosclerosis, meaning that when cardiac arrest occurs in these patients, it is typically more severe, and even if circulation is restored, organ recovery remains challenging. In summary, a high CHA_2DS_2-VASc score identifies a physiologically fragile subgroup with an increased risk of poor outcomes after ECPR.

Although the SAVE score clearly outperformed CHA_2DS_2-VASc in our analysis, patients requiring emergent ECMO often present with limited real-time data, making a fast and feasible scoring tool valuable in early decision-making, triage, or counseling. The SAVE score requires specific ECMO-related variables that may not be immediately accessible at the time of emergent cannulation, whereas the CHA_2DS_2-VASc score relies on chronic patient factors (age, sex, and comorbid conditions) and can be readily calculated by most clinicians familiar with cardiology risk assessment. Given that vascular comorbidities, advanced age, and chronic disease burden are major contributors to mortality in VA-ECMO patients,[31,34-36] the CHA_2DS_2-VASc score could be a useful tool for predicting survival in this setting. While the CHA_2DS_2-VASc cutoff value of ≥2 identified in the ROC analysis aligns with the threshold reported in the ESC atrial fibrillation (AF) guidelines,[21] its sensitivity and specificity differ across various patient populations.[42,43] In the OHCA setting, the CHA_2DS_2-VASc score may provide risk stratification with varying sensitivities and specificities at different threshold values. This emphasizes the need for further studies in larger, multicenter VA-ECMO cohorts to identify alternative cutoff points that ensure the most accurate balance between sensitivity and specificity. Nonetheless, our results suggest that once the CHA_2DS_2-VASc score reaches ≥2, the patient's cumulative comorbidity burden becomes a significant predictor of adverse outcomes in this emergent setting.

Limitations

This study has several limitations. First, it is a single-center, retrospective study with a relatively small sample size, which may limit the generalizability of the findings to broader OHCA cohorts, restrict causal inferences, and increase the risk of type II errors. Second, long-term outcomes of the patients were not assessed, preventing an evaluation of the extended prognostic impact of CHA_2DS_2-VASc score. Third, our study excluded certain extremely high-risk patient, such as those with advanced multi-organ failure, myocarditis, or prior heart/lung transplantation, conditions that overlap with critical components of the SAVE score. This exclusion might have contributed to the underrepresentation of patients with higher SAVE scores, which could have influenced the predictive performance. Lastly, other ECMO-specific scoring

systems were not included in the comparative analysis, which could have provided a more comprehensive assessment of risk stratification in this patient population. To address these limitations, larger, multicenter, prospective studies with long-term follow-up and external validation are needed to further investigate the prognostic utility of CHA_2DS_2-VASc and SAVE scores in ECMO patients.

CONCLUSION

This study demonstrates that the CHA_2DS_2-VASc score, while originally developed for thromboembolic risk assessment in atrial fibrillation, may serve as a valuable adjunctive tool for mortality prediction in patients undergoing VA-ECMO after cardiac arrest. Together with established ECMO-specific indices such as the SAVE score, CHA_2DS_2-VASc can contribute to a more accurate risk stratification and guide clinical decision-making. However, it remains crucial to integrate this information with a comprehensive clinical assessment and acute arrest-related factors.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Lokman Hekim University Non-interventional Clinical Researches Ethics Committee (Date: 30.12.2024, Decision No: 2024/13)

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Dental implant treatment from the patient's perspective: a descriptive, survey-based cohort study

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ABSTRACT

Aims: The aim of this study was to assess the participants' general knowledge and awareness about dental implants.

Methods: 550 voluntary participants over 18 years of age with or without missing teeth were applied to our clinic in 2024. The questionnaire was designed as multiple-choice.

Results: 550 volunteers, 282 females (51.19%) and 268 males (48.81%), participated in the study. 428 participants reported having missing teeth, while 120 participants reported having no missing teeth. Most participants (84.9%) thought missing teeth should be treated, while 14.2% thought missing teeth should not be treated. While 23.1% of the participants thought they had sufficient information about dental implants, 70.9% knew dental implants were a treatment alternative for missing teeth. While 41.6% of the participants stated that they obtained their current knowledge about dental implants from dentists, the rate of obtaining information from friends and relatives was 26.7%. 53.3% of the participants stated they feared dental implant treatment. Participants noted that the most positive factor affecting their decision to have dental implant treatment was better chewing, with 26.6%. Participants noted that the biggest challenge in choosing dental implant treatment was the high cost, 44%. 60% of the participants said oral, dental, and maxillofacial surgeons were the most qualified for dental implant treatment.

Conclusion: The study's results show that the level of awareness about dental implant treatment has increased but is still insufficient. Therefore, dentists should inform patients more about dental implant treatment to increase awareness further.

Keywords: Awareness, knowledge, dental implants, dental implantation, information source

INTRODUCTION

Artificial devices placed in tissues to restore a missing area in the human body or to heal a damaged organ are called implants.[1] The aim of modern dentistry is to restore the patient to his normal function, aesthetics, speech, and health. Dental implants, which allow us to achieve these goals ideally, are now used in the prosthetic treatment of completely or partially edentulous patients.[2] Numerous studies on the long-term successful outcomes of oral rehabilitation with dental implants have led to the widespread acceptance and popularity of dental implants in dentistry in recent years.[3,4] High patient satisfaction with dental implant treatment has been reported in the literature.[5-7] However, many patients still do not prefer this form of treatment. This is mainly because patients are less aware of dental implants.[8] In the literature, many surveys have been conducted to evaluate awareness about dental implant treatment.[9-12] Al-Johany et al.[9] conducted a survey study on dental patients in Riyadh and showed an acceptable level of awareness about dental implants. According to a study conducted in Dharwad, most patients were aware of dental implants as a treatment modality.[10]

There are also studies conducted in our country. Still, patients' knowledge level about dental implant treatments and their awareness of this treatment varies according to region, socioeconomic status, and years.[13-18] Yerliyurt et al.[13] showed that patients had insufficient knowledge about dental implants according to their study conducted in the same city as ours. Özkan Şen et al.[15] stated that patients had limited awareness about dental implant treatment in Konya. Memiş et al.[18] showed that patients had insufficient knowledge about dental implants, and awareness of patients was not high in the Western Black Sea Region of Turkey.

This study aims to evaluate the awareness and knowledge of patients living in Tokat about dental implants, which are used as a treatment method in rehabilitating lost/missing teeth, considering the data of 2024.

METHODS

The study was approved by the Non-interventional Clinical Researches Ethics Committee of Tokat Gaziosmanpaşa University (Date: 21.12.2023, Decision No: 23-KAEK-318). The surveys were conducted on patients who applied to Tokat

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Gaziosmanpaşa University, Faculty of Dentistry, Oral and Maxillofacial Surgery clinic in 2024. Our study was carried out in accordance with the Declaration of Helsinki. Individuals who have not received implant treatment before, have/do not have missing teeth, can read and write, can understand, and who volunteered for the study were included in the study. Individuals who refused to participate in the study, received dental implant treatment, and had no ability to read, write, and understand were excluded from the study. It was administered to adult and volunteer patients to participate in the study. Power analysis was performed using G*power Version 3.1.9.6 software. Power analysis was performed based on the educational level of the individuals and their answers to the question, "Are dental implants a treatment alternative for missing teeth?". According to the results of the chi-square test power analysis with 95% confidence (1-α), 95% test power (1-β), and w=0.202 effect size, it was concluded that research should be conducted on 512 cases. It was applied to 550 participants, considering possible losses. The questionnaire consists of 24 questions. The questionnaire includes questions that evaluate the demographic information of the volunteers, their knowledge, opinions and awareness about dental implants.

Statistical Analysis

Descriptive analyses were performed to give information about the general characteristics of the study groups. IBM SPSS V22 (IBM company, V22.0, Chicago, IL, USA) software was used for statistical analysis. Data on categorical variables are given as n (%). The significance test of difference and One-Way analysis of variance was used. Crosstabs and chi-square tests were used to assess whether there was a relationship between qualitative variables.

RESULTS

A total of 550 volunteers, 282 women (51.19%) and 268 men (48.81%) participated in the study. The demographic data of the volunteers are shown in Table 1.

Table 1. Demographic data of the participants

Demographic data		
	n	**%**
Gender		
Female	282	51.19
Male	268	48.81
Age		
30 and younger	175	31.75
31-36	83	15.14
37-42	75	13.69
43-49	88	16.06
50 and older	129	23.36
Education status		
Primary school	139	25.36
Secondary school	74	13.5
High school	137	25
University	169	30.48
Master	28	5.11
Doctorate	3	0.55
Income level		
10000 and less	176	31.73
10000-20000	175	32.28
20000-30000	71	13.17
30000 above	128	22.82
Marital status		
Married	381	69.45
Single	169	30.55

n: Number, %: Percent

While 428 participants stated that they had missing teeth, 120 stated that they did not. 27.3% of those with missing teeth were 50 or older, 24.5% were 30 and younger, and 48.2% were between 30 and 50. There is a statistically significant difference between age and the presence of missing teeth. While 94.2% of primary school graduates had missing teeth, it was observed that this rate decreased as the level of education increased. It was observed that only 30.4% of those with missing teeth were at university or higher education level. It was determined that 75.9% of those with missing teeth were married, and 24.1% were single. While the majority of the participants (84.9%) think that missing teeth should be treated, 14.2% think it is unnecessary to treat missing teeth. As age increases, the proportion of those who think missing teeth should be treated increases. When the question of whether you think missing teeth should be treated according to age groups was evaluated, there was a statistically significant difference between the groups. There is a significant difference between the participants under the age of 30 and those over the age of 50 who think that missing teeth should be treated ($p<0.001$) (Table 2).

While the rate of those who want to have dental implant treatment if deemed necessary is 60.5%, it is seen that 17.1% do not wish to have it done, and 20.9% are undecided. 38.3% of those who wish to have dental implants are university graduates. While 48.4% of those who do not wish to have dental implant treatment have an income level of 10.000 Turkish Liras or less, 73.9% of those who wish to have it have an income of 10.000 Turkish Liras or more.

53.3% of the participants stated they feared dental implant treatment. 62% of those who are afraid are women. When the answers to the question "Are you afraid of dental implant treatment?" were analyzed according to gender, a statistically significant difference was found between males and females ($p<0.001$) (Table 3). Most who are not afraid (53.6%) are university graduates.

While 23.1% of the participants thought that they had sufficient knowledge about dental implants, 70.9% of the participants knew that dental implants were a treatment alternative in the treatment of missing teeth. 57.5% of those who thought they had sufficient knowledge about dental implants were male, and 42.5% were female. It was observed that 40.9% and 36.2% of those who thought they had sufficient knowledge about dental implants and that dental implants were treatment alternatives for missing teeth were university

Table 2. Comparison of age groups according to the survey

		Age groups					
		30 and younger	31-36	37-42	43-49	50 and older	p
Do you think missing teeth should be treated? (n=540)	Yes	136 (78.2)[a]	66 (80.5)[a]	64 (85.3)[a,b]	77 (88.5)[a,b]	123 (96.1)[b]	<0.001
	No	38 (21.8)[a]	16 (19.5)[a]	10 (13.3)[a,b]	8 (9.2)[b]	5 (3.9)[b]	
Would you like to have dental implant treatment if it is deemed necessary? (n=547)	Yes	112 (64.4)	54 (65.1)	48 (64)	46 (52.3)	72 (56.7)	p=0.058
	No	21 (12.1)	10 (12)	11 (14.7)	20 (22.7)	31 (24.4)	
	Undecided	41 (23.6)	18 (21.7)	14 (18.7)	19 (21.6)	23 (18.1)	
Do you think you have enough information about dental implants? (n=544)	Yes	50 (29.1)[a]	22 (26.5)[a,b]	15 (20)[a,b]	21 (24.1)[a,b]	18 (14.1)[b]	p=0.048
	No	122 (70.9)[a]	61 (73.5)[a,b]	60 (80)[a,b]	65 (74.7)[a,b]	110 (85.9)[b]	
Do you know that dental implants are a treatment alternative for missing teeth? (n=538)	Yes	136 (78.2)	58 (69.9)	52 (69.3)	58 (65.9)	85 (66.4)	p=0.72
	No	36 (20.7)	24 (28.9)	21 (28)	27 (30.7)	41 (32)	
What are the limitations in choosing dental implants? (n=534)	High cost	69 (40.8)	42 (50.6)	30 (41.1)	34 (40.5)	67 (53.2)	p=0.384
	Less information	44 (26)	14 (16.9)	16 (21.9)	21 (25)	18 (14.3)	
	Surgery	31 (18.3)	15 (18.1)	13 (17.8)	12 (14.3)	15 (11.9)	
	Long treatment time	24 (14.2)	12 (14.5)	14 (19.2)	17 (20.2)	26 (20.6)	
How long do you think a dental implant will last? (n=535)	5	35 (20.5)	9 (10.8)	11 (15.1)	19 (22.6)	19 (15.3)	p=0.207
	10	52 (30.4)	26 (31.3)	22 (30.1)	25 (29.8)	32 (25.8)	
	20	39 (22.8)	15 (18.1)	16 (21.9)	15 (17.9)	19 (15.3)	
	Lifetime	45 (26.3)	33 (39.8)	24 (32.9)	25 (29.8)	54 (43.5)	
Do you think dental implants need special care and hygiene? (n=544)	Like natural teeth	50 (28.7)[a]	26 (32.1)[a]	27 (36)[a]	22 (25.3)[a]	38 (29.9)[a]	p=.001
	More than natural teeth	109 (62.6)[a,b]	51 (63)[a,b]	39 (52)[a,b]	58 (66.7)[b]	59 (46.5)[a]	
	Less than natural teeth	15 (8.6)[a]	4 (4.9)[a]	9 (12)[a,b]	7 (8)[a]	30 (23.6)[b]	

p<0.05 indicates significance among groups. p value from X^2 test. Data in parentheses represent percentages. The same letters represent similarity and different letters represent difference

Table 3. Comparison of gender groups according to the survey

		Sex		p
		Female	Male	
Do you have any missing tooth (s)? (n=547)	Yes	215 (76.8)	211 (79)	p=0.528
	No	65 (23.2)	56 (21)	
Would you like to have dental implant treatment if it is deemed necessary? n=539)	Yes	156 (55.7)	175 (65.8)	p=0.119
	No	54 (19.3)	40 (15)	
	Undecided	67 (23.9)	47 (17.7)	
Do you know that dental implants are a treatment alternative for missing teeth? (n=537)	Yes	196 (70)	193 (72.3)	p=0.063
	No	83 (29.6)	65 (24.3)	
What are the limitations in choosing a dental implant? (n=534)	High cost	117 (42.5)	123 (47.3)	p=0.418
	Less information	58 (21.1)	56 (21.5)	
	Surgery	51 (18.5)	35 (13.5)	
	Long treatment time	49 (17.8)	45 (17.3)	
Do you think dental implants need special care and hygiene? (n=543)	Like natural teeth	76 (27.4)	88 (33.1)	p=0.259
	More than natural teeth	170 (61.4)	145 (54.5)	
	Less than natural teeth	31 (11.2)	33 (12.4)	
Are you afraid of the dental implant treatment procedure? (n=535)	Yes	176 (63.8)[a]	108 (41.4)[a]	<0.001
	No	100 (36.2)[b]	151 (57.9)[b]	
What is the most important factor when deciding to have dental implants? (n=522)	Cost	103 (38.3)[a]	134 (52.1)[a]	p=0.006

p<0.05 indicates significance among groups. p value from X^2 test. Data in parentheses represent percentages. The same letters represent similarity and different letters represent difference

graduates. When the answers to the question "Do you think you have enough information about dental implants?" were examined according to age groups, it was seen that there was a significant difference between individuals under the age of 30 and over the age of 50 (p=0.048) (Table 2).

Participants stated that the most positive factor affecting their decision to have dental implant treatment was better chewing, with 26.6%. This is followed by the absence of the need to wear traditional prostheses with 21.1%. The aesthetic expectation was the 3rd most positive factor, with 19.5%.

Participants stated that the greatest difficulty they faced in choosing dental implant treatment was the high cost, 44%. When the answer to the question "What factors influence you in deciding on dental implant treatment?" was analyzed according to gender, a statistically significant difference was found between males and females (p=0.006) (Table 3). While 69.9% of the participants noted that everyone with missing teeth should have access to dental implant treatment, 30.1% stated that only rich people should have access to dental implant treatment. While 34.1% of the participants thought implant treatment was affordable, 65.9% stated it was expensive.

Participants were asked what material the dental implant was made of. While 54.5% stated that they had no idea, the rate of those who stated that the dental implant was made of titanium was 22.7% (Table 4).

Table 4. Distribution of participants' answers to the question of what material dental implants are made of

What material dental implants are made of?		
	n	%
Titanium	128	23.06
Zirconium	47	8.67
Platin	25	4.61
Porcelain	48	8.31
No idea	302	55.35

n: Number, %: Percent

While 41.6% of the participants stated that they obtained their current knowledge about dental implants from dentists, the rate of obtaining information from friends and relatives was 26.7% (Table 5). 33.1% of the participants stated that the duration of use of dental implants is lifelong. While the number of people who think that dental implants require more care than natural teeth is 57.5%, 36% of those who think this way are university graduates, and 34.5% are under the age of 30. 30% of respondents think dental implants should be cleaned like natural teeth. When the answers given to the question of how dental implants should be cared for were examined according to age groups, it was seen that there was a significant difference between the groups (p<0.001) (Table 2).

While 43.2% of the participants did not know the difference between traditional prostheses and dental implant treatment, 39.9% stated that implant treatment was better than traditional prostheses. While 25.5% of those who do not know the difference between traditional prostheses and dental implant

Table 5. Distribution of respondents' answers to the question "How did you learn about dental implants?"

Where did you learn about dental implants?		
	n	%
Print media (newspapers, magazines, etc.)	48	8.58
Audiovisual media (radio, TV)	45	8.03
Internet	81	14.78
Dentists	229	41.79
Friends/relatives	147	26.82

n: Number, %: Percent

treatment are primary school graduates, 41.9% of those who state that dental implant treatment is better are university graduates.

60% of the participants stated that oral, dental, and maxillofacial surgeons are the most qualified for dental implant treatment. While 58.7% of the participants say that the shape of the dental implant is in the form of a screw, 29.5% state that they do not know the shape of the implant. 36.3% of those who say that the shape of the implant is in the form of screws are university graduates. The rate of those who say dental implants are placed in the jawbone in the oral cavity is 52%.

DISCUSSION

This study aimed to evaluate the awareness of patients who applied to our clinic about dental implants. Most patients have limited information about dental implant applications and their success. This problem is more pronounced in developing countries with insufficient education and awareness. A limited number of people in developing countries prefer dental implants, and many factors influence the choice of dental implant treatment as a treatment method in these countries.[19,20] Society's awareness and evaluations about oral implants are also affected by demographic variables such as age, gender, socioeconomic status, place of residence, and the sources from which people obtain information.[21] In this study, in line with the literature, it was determined that awareness about dental implant treatment was not related to education level.[15,18]

Dental implants are often used in the treatment of missing teeth. In the study conducted by Choudhary et al.[23] in India, 23.24% of the participants saw dental implants as a treatment alternative for missing teeth; In the study of Tomruk et al.[22], which was conducted in our country 10 years ago, it was reported that 43.5% of the participants saw dental implants as a treatment alternative for missing teeth. In this study, 60.5% of the participants stated that dental implants were a treatment alternative for missing teeth. The increase in this rate in previous years shows that the awareness of dental implant patients has increased even more.

Today, obtaining information about a subject that is parallel to technological developments has become very easy. In the studies of Memiş et al.[18] and Al-Johany et al.[9], the most common source of information about dental implant treatment was their friends and relatives. In our study, the

majority of the participants stated that they obtained their knowledge about dental implants from dentists, similar to the studies reported in the literature[9,13,15,18,22,24] and 26.7% stated that they obtained it from their friends and relatives. The rate of information obtained from the Internet ranked third among the participants. These results show that dentists and their relatives are an important information source for patients with a positive view of dental implant treatment. If specialist dentists provide patient information via the Internet, it may be possible to reach more people.

One of the limiting factors for patients in dental implant treatment is surgical treatment. 53.3% of the participants stated they feared dental implant treatment. 62% of those who were afraid were women. Most of those who were not afraid (53.6%) were university graduates. In the study of Al-Johany et al.[25], 41.4% of the participants reported that they were afraid of surgery. As the authors report, when patients hear the word surgery, they think they are going to have major surgery. If dental implant surgical steps are explained to patients in detail and attention is paid to the language of communication, patients' fear may decrease.[26]

Routine dental treatments in Turkey are covered by health insurance. Since health insurance does not cover implant treatments, it is one of the most costly treatments. Participants stated that the biggest difficulty they faced in choosing dental implant treatment was the high cost with a rate of 44%, which was in line with the results of previous studies.[9,14,15,22,27] In this study, it has been shown that dental implant treatments are not economical for most patients. Dental implant prices should be more accessible so patients can access dental implant treatments more easily. For this reason, it will be beneficial to develop further university-industry cooperation for the purpose of dental implant production.

In our survey, respondents were asked where dental implants were placed, and 52% said that dental implants were placed in the jawbone in the oral cavity. These results are similar to previous studies conducted by Pommer et al.[27] and in our country.[14,22] For patient information, there is a need for a more detailed explanation about where dental implants are located in the mouth.

While the number of people who think that dental implants require more care than natural teeth is 57.5%, 36% of those who think this way are university graduates, and 34.5% are under the age of 30. 30% of respondents think dental implants should be cleaned like natural teeth. Tepper et al.[28] and Alanazi et al.[29] reported that their study concluded that dental implants require more care than natural teeth compared to most patients, which aligns with our study.

The duration of use of dental implants is one of the important parameters for patients. In our study, 33.1% of the participants stated that the duration of use of dental implants is lifelong. In the study conducted by Özcan Küçük et al.[14], 20% of the participants thought that the dental implant would last more than 20 years, while 2% stated that they had no idea. In the study conducted by Tepper et al.[28], approximately half of the patients stated the implant life as 1-20 years. In the study conducted by Alanazi et al.[29], approximately 18% of the participants reported that the life of dental implants was longer than 25 years. In comparison, approximately 37% reported that it was between 10-15 years.[29] Over time, we can see that patients have more information about dental implants.

Participants were asked what material the dental implant was made of. While 54.5% stated that they had no idea, the rate of those who stated that the dental implant was made of titanium was 22.7%. In the study conducted by Memiş et al.[18], more than half of the participants reported that they did not know what material the dental implant was made of. In the study conducted by Deeb et al.[30] in the United States, most participants reported that they did not know what material the dental implant was made of. While 58.7% of the participants said that the shape of the dental implant was in the form of a screw, 29.5% said that they did not know the shape of the implant. 36.3% of those who said that the shape of the implant was in the form of screws were university graduates. There is no data on the shape of the implant in the studies conducted in the literature. According to the results, it is thought that when informing about the dental implant, it should be emphasized what material it is made of and the shape of the implant.

In our country, non-specialists and specialist dentists can apply dental implant treatments. Most participants stated that oral and maxillofacial surgeons are the most qualified staff in dental implant placement, similar to previous studies.[18,30] It can be said that patients act consciously in this regard.

According to the data in our study, 43.2% of the participants did not know the difference between traditional prostheses and implant treatments. In comparison, 39.9% stated implant treatment was better than traditional prostheses. Participants cited better chewing as the most positive factor in the decision to have dental implants, followed by the absence of the need to wear dentures. The aesthetic expectation was the third positive factor. In the study conducted by Ho et al. with 1172 people in Japan, they reported that the most common reason for having dental implants was not using removable dentures and an increase in chewing.[12] In other studies, in line with our study, participants found implant treatment more acceptable and aesthetic than traditional prostheses.[9,22,24]

Limitations

This study has some limitations. Since the participants live in the same city, the general population will not capture the results. The region where the study was conducted may affect the results because demographic factors like education level, economic factors, and people's awareness in each region in Turkey are different. If the sample size in the subgroup of demographic data is selected like each other and researchers from different regions of the country come together and conduct joint studies, the study results may be less affected by demographic data and regions. Since there were only multiple-choice questions, the participants' personal opinions could not be examined in depth. We would like to state that the questionnaire used in the study is a questionnaire whose validity and reliability have not been demonstrated before.

CONCLUSION

According to the results of our study, the participants had a level of knowledge and awareness about dental implants. Still, information about the implant material, shape, where it was placed, and surgery should be done in more detail. Participants want to have dental implants in case of missing teeth, but they have difficulty accessing this treatment due to reasons such as economic difficulties and fear of surgery. Implants are frequently preferred today to restore function and aesthetics in the mouth and are now included in dentistry as a classic form of treatment. For this reason, for everyone to benefit from this treatment, we dentists should explain it to our patients in detail and eliminate their fears and concerns. Health policies need to be further developed to address treatment costs. Nationwide studies are needed to cover the general population and examine patient opinions.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Non-interventional Clinical Researches Ethics Committee of Tokat Gaziosmanpaşa University (Date: 21.12.2023, Decision No: 23-KAEK-318).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Association between leukocyte-based inflammatory indices and bone mineral density in hemodialysis patients

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ABSTRACT

Aims: Osteoporosis and osteopenia are common among hemodialysis (HD) patients, yet current methods for risk stratification remain limited. This study aimed to investigate the relationship between leukocyte-based inflammatory indices and osteoporosis and osteopenia in HD patients and to assess their diagnostic performance in differentiating these conditions.

Methods: A retrospective analysis was conducted on 168 HD patients classified into normal bone mineral density (BMD) (n=43), osteopenia (n=70), and osteoporosis (n=55) based on T-scores by dual-energy X-ray absorptiometry measurements. The leukocyte-based inflammatory indices were calculated as follows: Platelet to lymphocyte ratio (PLR)=platelet count/ lymphocyte count ratio; neutrophil o lymphocyte ratio (NLR)=neutrophil count/ lymphocyte count ratio; systemic immune inflammation index (SII)=platelet count×neutrophil count / lymphocyte count ratio, and systemic inflammation response index (SIRI)=neutrophil count×monocyte count/ lymphocyte count ratio.

Results: Osteopenia and osteoporosis were identified in 41.7% and 32.7% of patients, respectively. Patients with osteoporosis exhibited higher neutrophil and monocyte counts and lower lymphocyte counts ($p<0.001$). All inflammatory indices were higher in osteoporosis group compared to other group. Also, these indices were higher in osteopenia group compared to normal BMD group. SIRI showed the strongest discriminative power for differentiating osteopenia from normal BMD (AUC=0.84; sensitivity=81.4%; specificity=79.2%, $p<0.001$) and osteoporosis from osteopenia (AUC=0.86; sensitivity=82.5%; specificity=78.6%; $p<0.001$).

Conclusion: Leukocyte-based inflammatory indices, particularly SIRI, are significantly associated with reduced BMD in HD patients and may serve as accessible biomarkers for identifying those at heightened risk of osteopenia and osteoporosis.

Keywords: Bone mineral density, hemodialysis, osteoporosis, systemic inflammation

INTRODUCTION

Chronic kidney disease (CKD) is a global health concern that affects millions of people and is associated with various complications, including mineral and bone disorders (CKD-MBD).[1] Among patients with end-stage renal disease (ESRD) receiving hemodialysis (HD), disturbances in bone mineral density (BMD) are particularly common, leading to an increased risk of osteoporosis and fractures.[2] The underlying pathophysiology of these skeletal complications is multifactorial and includes altered calcium-phosphorus metabolism, vitamin D deficiency, abnormalities of parathyroid hormone (PTH), and chronic inflammation.[3]

The connection between bone health and inflammation is well-demonstrated in the process of bone fracture healing, which represents a classic acute inflammatory response driven by the innate immune system.[4,5] At the fracture site, both bone-forming cells and immune cells are actively recruited, leading to a complex interplay between hematopoietic stem cell-derived lineages (monocytes, macrophages, osteoclasts) and mesenchymal stem cell-derived lineages (pre-osteoblasts, osteoblasts). This dynamic interaction highlights the crucial role of inflammation in bone remodeling and regeneration.[6,7] In patients suffering from chronic inflammation, such as CKD, persistent cytokine activation further disrupts bone homeostasis.[8,9] Pro-inflammatory cytokines stimulate osteoclast differentiation and activity, leading to increased bone resorption, while simultaneously inhibiting osteoblast function and bone formation. This imbalance accelerates bone loss and contributes to the development of osteoporosis.[10]

Recent studies have proposed leukocyte-based inflammatory indices, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune inflammation index (SIRI), as potential markers for systemic inflammation in various disease states, including CKD and osteoporosis.[11-13]

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However, the diagnostic performance of these leukocyte-based inflammatory indices, including SIRI, in distinguishing patients with osteopenia or osteoporosis has not been comprehensively investigated. This study aimed to investigate the relationship between leukocyte-based inflammatory indices and osteoporosis and osteopenia in HD patients and to assess their diagnostic performance in differentiating these conditions.

METHODS

Ethics

This retrospective study was carried out at the Başkent University Practice and Research Hospital Orthopedic Clinic between January 2018 and January 2023, adhering to the ethical principles outlined in the Declaration of Helsinki. Approval was obtained from the Başkent University Hospital Medicine and Health Sciences Ethics Committee (Date: 22/10/2024, Decision No: KA24/346). Given the retrospective nature of the study, the Local Ethics Committee waived the requirement for informed consent.

Study Population

During the study period, 216 HD patients who were followed up in the orthopedic clinic for bone health were retrospectively assessed for study eligibility. The inclusion criteria included that patients must be over 18 years old, have received HD for at least six months, and have bone densitometry measurements available. The exclusion criteria were patients with active infection, recent surgery, known inflammatory diseases unrelated to CKD, cardiac conditions such as atrial fibrillation, aortic stenosis, or myocardial infarction, uncontrolled hypertension (>180/100 mmHg), a history of acute respiratory failure or thromboembolism, a history of autoimmune disease or malignancy, and those receiving corticosteroids or other immunosuppressive treatments. After applying the exclusion criteria, 168 patients were included in the final analysis.

Study Protocol

Demographic, and clinical data were collected from electronic patient records. Hypertension was defined by a blood pressure measurement exceeding 140/90 mmHg or the administration of antihypertensive medications, whereas diabetes mellitus was identified based on a fasting plasma glucose level of ≥126 mg/dl or the use of antidiabetic agents. Biochemical parameters were obtained from patient records of venous blood samples collected during outpatient evaluations at the time of hospital admission. All analyses were conducted in a single laboratory using standardized methodologies, as summarized below.

Biochemical Analysis

Data on laboratory parameters were retrospectively retrieved from venous blood samples obtained at the time of hospital admission. Hematological parameters were evaluated through laser and impedance-based methods with the CellDyn Ruby hematology analyzer (Abbott Diagnostics, Abbott Park, Illinois, USA) device. The assessment of biochemical parameters was performed using commercial kits and an Architect C8000 and i2000 autoanalyzers (Abbott Diagnostics, Abbott Park, Illinois, USA). The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C).[14] Inflammation indices were calculated as follows: PLR=platelet count/lymphocyte count; NLR=neutrophil count/lymphocyte count; SII=platelet count×neutrophil count/lymphocyte count, and SIRI=neutrophil count×monocyte count/lymphocyte count.

BMD Examination

BMD measurements had been previously performed using a Hologic QDR 4500 Densitometer Machine (Hologic Inc., Bedford, MA, USA) by trained technicians, following the manufacturer's standardized protocol for imaging and analysis. The BMD assessments were conducted at two key skeletal sites: the lumbar spine (anteroposterior projection at L1–L4) and the femoral neck (FN). The World Health Organization classification system was used to categorize patients into the normal (-1≤ T-score), osteopenia (-2.5< T-score <-1), and osteoporosis (T-score ≤-2.5) groups.[15]

Statistical Analysis

All data were analyzed with STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation values, while non-normally distributed variables are given as median (25^{th}-75^{th} quartiles) values. ANOVA test (post-hoc: Bonferroni test) or Kruskall-Wallis H test (post-hoc: Dunn's test) were used for comparisons between more than two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher-exact tests. Multivariable logistic regression analysis with the backward Wald method was performed to identify any possible independent predictors of osteoporosis and osteopenia. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance, and the results of area under the curve (AUC), standard error (SE), and sensitivity and specificity are reported. The optimal threshold value of the inflammation indices was determined by the Youden index method. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULTS

The mean age of HD patients was 57.0±10.2 years (range: 36–70), with the majority being male. Hypertension was present in 63.7% of patients, diabetes mellitus in 25.6%, and coronary artery disease in 14.9%. The median HD duration was 3.5 years. Normal BMD was detected in 25.6% of patients, while 41.7% had osteopenia and 32.7% had osteoporosis. There were no significant differences in demographic characteristics among the normal BMD, osteopenia, and osteoporosis groups (Table 1).

Table 2 presents the comparison of laboratory parameters among HD patients with normal BMD, osteopenia, and osteoporosis. Systemic inflammatory indices were higher in the osteoporosis group compared to other groups. Also, these indices were higher in the osteopenia group compared to normal BMD group (SIRI→ normal: 0.4±0.2 vs. osteopenia: 0.8±0.2 vs. osteoporosis: 1.2±0.4, $p<0.001$; SII→ normal: 401.6±104.5 vs. osteopenia: 473.2±115.2 vs. osteoporosis:

Table 1. Demographic and clinical characteristics of hemodialysis patients

Variables	Normal	Osteopenia	Osteoporosis	p-value
	n=43	n=70	n=55	
Age, years	56.7±10.8	57.1±9.2	57.0±10.4	0.854
Gender, n (%)				
Female	19 (44.2)	28 (40.0)	17 (30.9)	0.352
Male	24 (55.8)	42 (60.0)	38 (69.1)	
BMI, kg/m^2	26.4±3.9	25.7±4.4	24.8±4.5	0.257
Smoking, n (%)	16 (37.2)	27 (38.6)	20 (36.4)	0.981
Hypertension, n (%)	25 (58.1)	44 (62.9)	38 (69.1)	0.536
Diabetes mellitus, n (%)	10 (23.3)	17 (24.3)	16 (29.1)	0.785
CAD, n (%)	7 (16.3)	7 (10.0)	11 (20.0)	0.288
HD duration, years	3.0 (1.0-5.0)	3.5 (1.0-5.5)	4.0 (1.0-6.5)	0.757
L1-L4 total T score	0.3 [(-0.2)-(1.2)]	-1.3 [(-1.5)-(-0.9)]	-2.9 [(-3.1)-(-2.7)]	<0.001*
Femur neck T score	0.4 [(-0.5)-(1.3)]	-1.3 [(-1.6)-(-0.8)]	-2.8 [(-3.0)-(-2.5)]	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Differences between groups are highlighted in bold characters. Abbreviations: BMI: Body-mass index, CAD: Coronary artery diseases, HD: hemodialysis

Table 2. Comparison of laboratory findings in hemodialysis patients with normal bone density, osteopenia, and osteoporosis

Variables	Normal	Osteopenia	Osteoporosis	p-value
	n = 43	n = 70	n = 55	
Leukocytes, ×10^9/L	7.3±1.7	7.0±1.4	6.7±1.9	0.197
Neutrophils, ×10^9/L	3.6±0.6	3.7±0.7	4.0±0.7	<0.001*
Lymphocytes, ×10^9/L	2.6±0.6	2.3±0.5	2.0±0.6	<0.001*
Platelets, ×10^9/L	256.4±60.0	259.2±65.3	269.8±55.7	0.485
Monocytes, ×10^9/L	0.4±0.2	0.5±0.2	0.6±0.2	<0.001*
NLR	1.5±0.4	1.7±0.5	2.0±0.6	<0.001*
PLR	108.7±35.1	126.0±34.7	148.6±41.0	<0.001*
SIRI	0.4±0.2	0.8±0.2	1.2±0.4	<0.001*
SII	401.6±104.5	473.2±115.2	536.8±145.6	<0.001*
Hemoglobin, g/dl	10.8±1.3	10.7±1.3	10.7±1.0	0.948
Total-C, mg/dl	158.5±44.9	155.5±41.1	148.7±48.9	0.529
LDL-C, mg/dl	101.4±32.9	102.1±34.4	97.1±35.1	0.703
HDL-C, mg/dl	37.3±11.1	36.3±9.6	36.7±12.0	0.901
Triglycerides, mg/dl	172.0 (132.0-216.5)	152.0 (92.8-204.8)	158.0 (119.0-228.0)	0.443
Total protein, g/dl	65.1±9.2	66.5±9.8	67.6±7.9	0.962
Urea, mg/dl	153.0 (116.0-198.5)	150.5 (127.2-186.8)	157.0 (134.0-191.0)	0.728
Creatinine, mg/dl	8.8±2.8	9.0±3.0	9.1±2.7	0.176
Uric acid, mg/dl	6.4±1.4	6.8±1.4	6.5±1.1	0.145
Calcium, mg/dl	8.6±0.9	8.4±0.8	8.4±0.6	0.261
Phosphorus, mg/dl	4.5±1.4	4.4±1.5	4.3±1.6	0.261
Albumin, g/dl	3.5±0.6	3.6±0.3	3.7±0.4	0.226
CRP, mg/dl	6.1 (3.1-11.4)	8.6 (4.3-13.1)	11.3 (6.1-16.2)	0.042*
Vitamin D, µg/L	23.0 (17.8-33.0)	19.0 (15.4-25.0)	16.5 (12.4-24.1)	0.087
PTH, ng/L	107.1 (28.5-331.6)	238.5 (62.1-530.5)	401.1 (266.2-661.2)	<0.001*

Data are mean±standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Differences between groups are highlighted in bold characters. Abbreviations: BMI: Body-mass index, CRP: C-reactive protein, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PTH: Parathyroid hormone, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, Total-C: Total cholesterol

536.8±145.6, p<0.001). The median CRP level was found to be higher in the osteoporosis group than in the other groups, while no statistically significant difference was observed between the osteopenia and normal groups (normal: 6.1 vs. osteopenia: 8.6 vs. osteoporosis: 11.3, p=0.042). The median PTH levels showed variation among all groups, with the osteoporosis group exhibiting the highest median value (normal: 107.1 vs. osteopenia: 238.5 vs. osteoporosis: 401.1, p<0.001) (Table 2).

The effects of leukocyte-based inflammation indices on osteoporosis and osteopenia are displayed in Table 3. In Model I regression analysis, the effects of age, sex, BMI, comorbid conditions, and HD duration were adjusted. In Model II regression analysis, in addition to the parameters in model I, the effects of CRP and PTH levels were also adjusted. In both adjusted regression models, leukocyte-based inflammation indices continued to have a significant impact on osteopenia and osteoporosis.

Table 4 summarizes the diagnostic performance of select laboratory parameters for differentiating patients with osteopenia from those with normal BMD and those with osteoporosis from osteopenic patients. Among these parameters, the SIRI emerged as the most robust indicator in both comparisons. For distinguishing osteopenia from normal BMD, SIRI had a threshold value of >0.57, with 81.4% sensitivity and 79.2% specificity (AUC±SE=0.84±0.04, 95% CI=0.77-0.91, p<0.001). For differentiating osteoporosis

Table 3. Impact of leukocyte-based inflammatory indices on osteopenia and osteoporosis in hemodialysis patients based on crude and adjusted models

Variables	Osteopenia			Osteoporosis		
	OR	95% CI	p-value	OR	95% CI	p-value
SIRI						
Crude	2.52	1.78-3.54	<0.001*	1.95	1.53-2.49	<0.001*
Adjusted model I	2.57	1.80-3.65	<0.001*	2.52	1.80-3.53	<0.001*
Adjusted model I	2.62	1.83-3.77	<0.001*	2.62	1.82-3.75	<0.001*
SII						
Crude	1.05	1.01-1.07	0.001*	1.03	1.01-1.05	<0.001*
Adjusted model I	1.05	1.01-1.08	0.008*	1.04	1.01-1.07	0.004*
Adjusted model I	1.05	1.03-1.08	0.007*	1.04	1.01-1.06	0.007*
NLR						
Crude	3.50	1.11-8.08	0.001*	3.09	1.48-6.45	0.003*
Adjusted model I	3.93	1.27-12.16	0.018*	3.24	1.47-7.56	0.005*
Adjusted model I	3.75	1.21-11.61	0.022*	3.36	1.08-10.48	0.007*
PLR						
Crude	1.02	1.01-1.03	0.001*	1.02	1.01-1.03	0.001*
Adjusted model I	1.02	1.01-1.03	0.008*	1.03	1.01-1.04	0.008*
Adjusted model I	1.03	1.01-1.04	0.007*	1.03	1.01-1.05	0.013*

Abbreviations: CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, OR: Odds ratio

Table 4. Diagnostic performance of laboratory parameters associated with osteopenia and osteoporosis

Variables		AUC±SE	95% CI	Sens. (%)	Spec. (%)	Threshold	p-value
Osteopenia *vs.* control	Neutrophils	0.53±0.06	0.42-0.64	22.9	90.7	>3.5	0.617
	Lymphocytes	0.63±0.06	0.53-0.736	71.2	67.8	<2.4	0.020*
	Monocytes	0.68±0.04	0.60-0.75	70.5	68.4	<0.5	<0.001*
	SIRI	0.84±0.04	0.77-0.91	81.4	79.2	>0.57	<0.001*
	SII	0.72±0.06	0.61-0.82	70.1	69.2	>438.4	0.001*
	NLR	0.68±0.05	0.59-0.78	65.4	67.3	>1.53	0.001*
	PLR	0.66±0.05	0.57-0.77	62.4	63.6	>118.4	0.001*
	CRP	0.50±0.06	0.39-0.61	67.1	45.8	>6.5	0.488
	PTH	0.62±0.06	0.52-0.73	70.4	71.3	>188.4	0.027*
Osteoporosis *vs.* osteopenia	Neutrophils	0.68±0.05	0.57-0.7	68.9	67.4	>3.7	0.909
	Lymphocytes	0.65±0.05	0.56-0.75	70.4	69.8	<2.1	0.002*
	Monocytes	0.70±0.04	0.62-0.79	64.5	78.2	>0.6	0.001*
	SIRI	0.86±0.03	0.78-0.94	82.5	78.6	>1.0	<0.001*
	SII	0.71±0.05	0.62-0.79	70.2	58.6	457.8	<0.001*
	NLR	0.68±0.05	0.58-0.75	58.2	75.7	>1.9	0.001*
	PLR	0.67±0.05	0.57-0.75	50.1	84.3	>140.9	<0.001*
	CRP	0.66±0.05	0.56-0.76	70.4	45.7	>9.0	0.045*
	PTH	0.69±0.05	0.59-0.579	76.9	51.4	>254.3	0.032*

*p<0.05 indicates statistical significance. Abbreviations: AUC: Area under the curve, CI: Confidence interval, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PTH: Parathyroid hormone: Sens: Sensitivity, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, Spec: Specificity

from osteopenia, the threshold value was >1.0, with 82.5% sensitivity and 78.6% specificity (AUC±SE=0.86±0.03, 95% CI=0.78-0.94, p<0.001) (**Figure**).

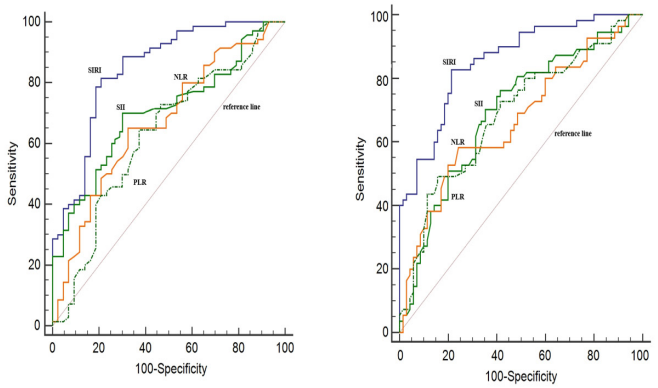

Figure. Diagnostic performance of leukocyte-based inflammatory indices in differentiating osteopenia (*vs.* normal bone mineral density) and osteoporosis (*vs.* osteopenia)

DISCUSSION

Osteoporosis and osteopenia are highly prevalent in HD patients, with some studies reporting rates exceeding 16–41% for osteoporosis and 32-52% for osteopenia.[2,16-19] The frequencies rates observed in this study were in agreement with findings from the existing literature. The mechanisms underlying osteoporosis and osteopenia in dialysis patients are multifactorial, falling under the umbrella of CKD-MBD. As kidney function declines, disturbances in mineral homeostasis and bone turnover develop early and worsen progressively.[20,21] Secondary hyperparathyroidism serves as a central mechanism, driven by diminished renal phosphate excretion and impaired synthesis of active vitamin D (calcitriol), culminating in hyperphosphatemia, hypocalcemia, and vitamin D deficiency. These changes trigger excess PTH secretion, which in turn stimulates osteoclast activity and bone resorption.[22,23] In agreement with these findings, HD patients, especially those with osteoporosis, were found to have lower vitamin D levels and higher PTH levels.

HD patients typically exhibit a chronic pro-inflammatory state, which is common in ESRD.[24] The bone and immune systems are tightly interconnected (osteoimmune regulation), meaning immune cell activity can directly influence bone remodeling.[25] In dialysis patients, who often have a sustained inflammatory burden, there is strong biologic plausibility that inflammation contributes to accelerated bone loss.[26] Immune cells and their cytokines can alter osteoclast and osteoblast function, affecting BMD.[27] Iron overload-induced osteoporotic mice exhibited a significant increase in leukocyte counts and their subtypes. Similarly, the same study reported comparable findings in osteoporotic patients relative to healthy controls.[28]

A growing body of evidence links higher leukocyte counts or imbalanced differentials to lower BMD.[28-30] Nonetheless, leukocyte subtypes may not serve as consistent predictors of BMD and clinical assessments of microarchitecture. A population-based prospective study found that in postmenopausal women enrolled between 2009 and 2012, only neutrophils demonstrated an inverse association with BMD. In contrast, among those enrolled between 2014 and April 2017, both leukocytes and monocytes exhibited inverse relationships with BMD.[31] This is in agreement with the low diagnostic performance of leukocyte subtypes reported in the present study. Therefore, inflammation indices generated from leukocyte subtypes may demonstrate improved diagnostic performance. A meta-analysis found that NLR and PLR were higher in the osteoporosis group, regardless of gender. Additionally, in a subgroup analysis focusing on postmenopausal women, NLR was found to be associated with osteoporosis independently of age and comorbidities.[32] A study conducted on patients with ESRD found that NLR levels were not associated with BMD.[33] In a study involving HD patients, NLR and PLR levels were reported to show no significant difference between those with normal BMD and those with osteoporosis or osteopenia.[12] Discrepancies among studies may stem from differences in patient selection criteria, demographic characteristics, HD duration, and the distribution of comorbid conditions. In this study, although higher NLR and PLR levels were observed in HD patients with osteoporosis or osteopenia compared to those with normal BMD, their sensitivity in distinguishing these conditions was found to be low. In light of these findings, leukocyte-derived ratios such as NLR and PLR may have limited utility in assessing bone health in HD patients. Given the complex interplay between inflammation and bone metabolism, broader inflammatory indices, such as the SII and the SIRI, may offer a more comprehensive assessment of inflammatory burden and its impact on BMD.

A study analyzing 2.302 CKD patients from the NHANES cohort identified an inverse association between SII and BMD. Notably, higher SII levels remained predictive of lower pelvic BMD even after adjustments for age, sex, and race.[11] In the present study, all leukocyte-based inflammatory indices remained significant after adjusting for age and sex. Notably, SIRI demonstrated superior diagnostic performance, exhibiting higher sensitivity and specificity than other leukocyte-derived inflammatory markers in distinguishing osteopenia from normal BMD and osteoporosis from osteopenia in dialysis patients. This may be attributed to SIRI's incorporation of monocytes, a key cell type involved in chronic inflammation and osteoclast precursor supply.[34] On the other hand, this is the first study to evaluate the association between SIRI and bone loss in HD patients. Therefore, further research is needed to validate the diagnostic performance of SIRI in assessing bone loss in HD patients. However, in certain selected cohorts, the diagnostic performance of SIRI in predicting bone loss aligns with the current findings. An elderly hypertensive patient study demonstrated that SIRI was significantly associated with lower BMD, higher osteoporosis prevalence, and even higher fracture incidence during follow-up.[35] Similarly, a study in postmenopausal women reported a strong negative association between SII and BMD across quartiles, with those in the highest SII and SIRI quartile exhibiting significantly lower femoral neck BMD compared to those in the lowest quartile. Notably, after controlling for confounding factors, SII and SIRI remained a significant predictor of BMD in postmenopausal women but not in premenopausal women, highlighting its potential role in age-related bone loss.[36]

Limitations

This study has some important limitations. The primary limitation of this study is its single-center, retrospective design, which may restrict its generalizability to HD patients and hinder causal interpretations regarding the impact of elevated inflammation on bone loss. Second, a single measurement of leukocyte counts and BMD may not fully account for temporal fluctuations in inflammation or bone metabolism. Third, additional confounding variables, including nutritional status, dialysis adequacy, and specific treatments like vitamin D analogs, phosphate binders, or steroids, were not analyzed in this study. Lastly, assessments such as cytokine profiling and flow cytometry were not feasible due to the study's design. Longitudinal studies with large cohorts that incorporate these limitations are required.

CONCLUSION

This study highlights the significant role of systemic inflammation in the deterioration of BMD among HD patients. Elevated inflammatory indices were associated with both osteopenia and osteoporosis, suggesting that chronic inflammation may contribute to bone metabolism dysregulation in this population. Among leukocyte-based inflammation indices, SIRI has the potential to serve as a novel and accessible screening tool for identifying individuals at increased risk of osteoporosis and osteopenia. These findings emphasize the need to incorporate inflammatory markers into osteoporosis risk assessment strategies in this cohort.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval was obtained from the Başkent University Hospital Medicine and Health Sciences Ethics Committee (Date: 22/10/2024, Decision No: KA24/346).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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Original Article

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Fractal analysis of mandibular condyle trabecular structure in children

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ABSTRACT

Aims: The aim of this study was to investigate the changes in the trabecular structure of the mandibular condyle with age in children using fractal analysis (FA) on dental panoramic radiographs (DPRs) and to evaluate the fractal dimension (FD) differences according to age groups and gender.

Methods: In this retrospective study, 110 pediatric patients with DPR were divided into 2 groups according to age: 6-8 age group (n=55, mean: 6.8±0.704 years), 9-12 age group (n=55, mean: 11.18±1.775 years). FD values obtained from the right and left mandibular condyle were analyzed according to age and gender. For the calculation of FD, a 40x40 pixel square region of interest (ROI) was selected from the geometric center of both mandibular condyles. Image J version 1.52 software was used to obtain FD values by box counting method. Data were analyzed using IBM SPSS Statistics program. T-test was used to compare parametric data and Mann-Whitney U test was used to compare non-parametric data. Statistical significance level was determined as $p<0.05$.

Results: The mean FD of the right condyle was 1.046±0.086 and the mean FD of the left condyle was 1.201±1.205 in the 9-12 age group; the mean FD of the right condyle was 0.909±0.063 and the mean FD of the left condyle was 0.924±0.08 in the 6-8 age group. The mean FD values of both condyles increased with age and this increase was statistically significant ($p<0.001$). There was no significant difference between the mean FD values of the right and left condyles between genders in the same age group ($p>0.05$).

Conclusion: In the present study, FD values were determined for the trabecular structure of the mandibular condyle in healthy children. The results of the study showed that the FD values obtained from both mandibular condyles on DPRs in children increased with age.

Keywords: Fractal analysis, panoramic radiograph, pediatric patients

INTRODUCTION

The temporomandibular joint (TMJ) connects the mandible to the cranium with ligaments and muscles and provides bilateral articulation.[1-3] TMJ performs a crucial role in the facilitation of the jaw's range of motion to enable speaking, chewing, breathing and swallowing.[2] As sucking behavior at the beginning of life gradually transforms into masticatory movement, its evolution continues to adapt to the changing function of TMJ. TMJ's position between the skull base and mandible defines its growth and function.[4] In infants and 2-3 year olds, condyle neck is thick and short, cortical bone is thin, bone marrow is dense and the glenoid fossa is shallow. Similar to the adult anatomy, growth begins at 7-8 years of age.[5,6] The condyle continues to grow with bone apposition without losing its relationship with the glenoid fossa. Mandibular growth occurs from condylar growth center between the ages of 1-5 years, while active mandibular growth occurs between the ages of 10-15 years in relation to muscle function.[7]

At the same time as changes in the condyle, changes in occlusal forces cause microscopic and macroscopic changes in the jaw bones.[8] TMJ's mechanical characteristics such as strength, quality and resistance rely on thickness of the cortical bone of mandibular condyle, the intensity of trabecular bone and the composition of the trabeculae. Trabecular bone architecture has a structure suitable for load-bearing functions. Compared to cortical bone, trabecular bone has a greater metabolic activity, which is more indicative for assessing changes in osseous structure.[9,10]

Fractal analysis (FA) measured on dental panoramic radiographs (DPRs) is a popular method to quantitatively describe the quality of bone tissue, analyzing early changes in alveolar bone and mandibular trabecular architecture.[11,12] In trabecular bone, fractal dimension (FD) results calculated by the box counting method are assumed to be between 1

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and 2. Values closer to 2 represent a highly complex bone microstructure, while values closer to 1 represent simpler bone microstructures that emphasize the porosity of the bone.[13,14]

Despite the fact that DPRs are non-invasive techniques that are frequently utilized and provide early indication during dental diagnosis and treatment, dual-energy X-ray absorptiometry (DXA) is the most widely used densitometric technique for bone mineral density assessment worldwide and is preferred over other techniques due to its speed, sensitivity, safety, low cost and widespread availability. Additionally, DXA is considered the gold standard for the assessment of bone mineral density.[15]

Although DPRs are used routinely in dentistry for diagnosis and treatment, there are limited studies in the literature evaluating FA in pediatric patients using existing DPRs.[3,11,14,16] Understanding age-related changes in bone dynamics can provide significant clinical benefits in monitoring growth and development, planning orthodontic treatments, and early diagnosis of TMJ disorders. Investigating the applicability of FA on DPRs may contribute to the non-invasive assessment of bone structure in pediatric patients.

The aim of this study was to investigate the age-related alterations in the trabecular structure of the mandibular condyle with age in children using FA on DPRs and to assess the FD differences according to age groups and gender.

METHODS

The present retrospective study was executed in the Department of Dentomaxillofacial Radiology, Faculty of Dentistry, Ankara Medipol University, in full compliance with current ethical guidelines, which included the 1964 World Medical Association Declaration of Helsinki and its subsequent revisions. Prior to the study, ethics clearance was received from the Non-interventional Clinical Researches Ethics Board of Ankara Medipol University (Date: 06.06.2023, Decision No: 63). When preparing the dataset, the data was anonymized to prevent information about the patients' identity (except for age and gender) and no additional consent form was obtained from the patients.

This study included DPRs of a total of 220 patients 110 (48 girls, 62 boys) aged 6-8 years and 110 (56 girls, 54 boys) aged 9-12 years) who presented to the Department of Pediatric Dentistry, Faculty of Dentistry for routine oral and dental examinations. The anamnesis of the patients was checked through the patient registration system and patients without any systemic disease affecting the bone, without TMJ pain and craniofacial deformity, without a history of trauma and periodontal disease, and without congenital missing or extracted teeth have been included in that study. We excluded patients with any disease affecting the TMJ. In this regard, patients with inflammatory and infectious diseases such as Juvenile idiopathic arthritis (JIA), rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus (SLE) and septic arthritis as well as developmental anomalies such as hemifacial microsomia and condylar hypoplasia/hypertrophy were excluded. Additionally, patients with a history of functional disorders such as condylar fracture, TMJ dislocation, osteochondroma and bruxism were also excluded. Individuals with a history of orthodontic treatment and diagnosed malocclusion were also excluded. Subjects who did not have normal dentition for their age and subjects with DPRs of insufficient diagnostic quality were excluded from the study.

All DPRs were acquired with one appliance (Castellini X-Radius Tr10 Plus, Italy) utilizing 60-85 kVp, 4-8mA and 12.3 s exposure time. Each patient's DPRs were taken by the same radiology technologist. During acquisition, it was placed in accordance with the manufacturer's recommendations. Positions were set with Frankfurt horizontal plane parallel to the ground and sagittal plane adjusted in accordance with vertical line reproduced by device.

Fractal Analysis

FD was performed by box counting based on the method described by White and Rudolph.[17] Regions of interests (ROIs) were selected from the condyle region similar to the study of Tokuç et al.[3] in order to examine the change in the effect of growth and development on the condyle with age. For FD analysis, two ROIs of 40×40 pixels were chosen for each patient, the central region of the right (ROI-Rc) and left (ROI-Lc) mandibular condyle (Figure 1). FD was calculated using Image J version 1.52 (National Institutes of Health, Bethesda, MD, USA) software.

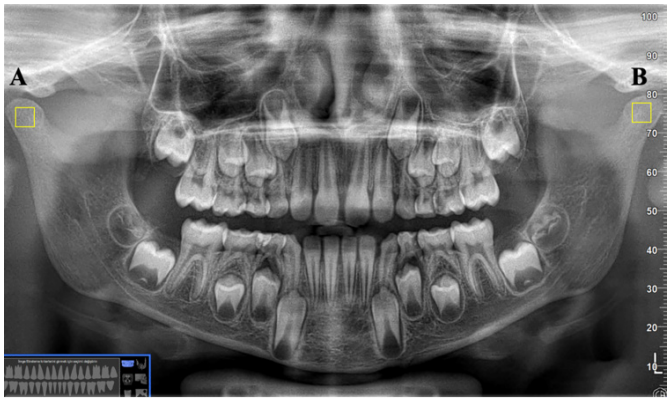

Figure 1. Selection of regions of interest in dental panoramic radiography. A: ROI-Rc. B: ROI-Lc
ROI-Rc: Central region of the right, ROI-Lc: Central region of the left

The image was replicated after selecting the ROI (Figure 2a). Gaussian filter was added to the image to create a blurring affect (Figure 2b). The emerging blurred image was subsequently extracted from the initial display (Figure 2c). In order to upgrade specific characteristics with different brightness degrees, like trabeculae and bone marrow, add 128 gray values to each pixel position to acquire a display (Figure 2d). The image was transformed into a binary format by applying a brightness value threshold of 128 (Figure 2e). In order to decrease noise, binary imaging was undergone a process of erosion and dilation (Figure 2f, 2g). The image was subsequently inversed, showing the trabecular areas in as the black and the bone marrow in white (Figure 2h). Eventually, this image was put through a skeletonization process that progressively removes pixels so that only a central line of pixels remains (Figure 2i). The software utilized an algorithm for box counting that split the image into frames of 2, 3, 4, 4, 6, 6, 8, 12, 16, 32, 64 pixels (Figure 2). The count of grids

comprising trabeculae and the total number of grids were measured for per pixel size. These values were represented on a graph with a logarithmic scale. In the graph, the slope of the curve of the line connecting the plotted points provided FD value.

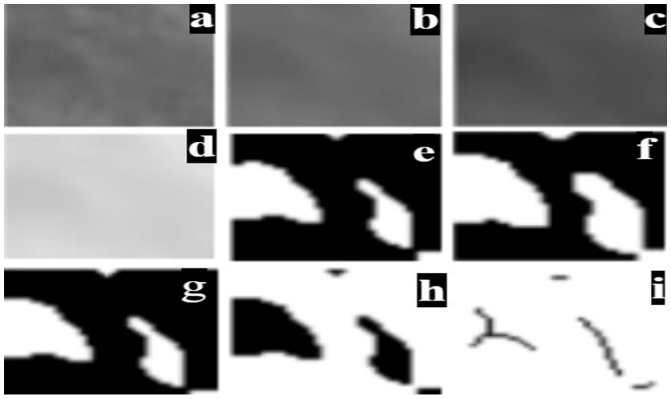

Figure 2. Fractal analysis **a**. Duplicated version of ROI **b.** Gaussian blur **c.** Subtraction **d.** Addition of 128 gray value **e.** Binarization **f.** Erosion **g.** Dilation **h.** inversion **i.** Skeletonization
ROI: Region of interest

FA calculations were conducted by a dentomaxillofacial radiologist with five years of experience (EMAO) who was blinded to participants' medical information. To improve intra-observer calibration and reliability of the assessments, 20% of the images were reviewed by the same observer two weeks after the initial assessment. The average of the results from the initial and subsequent measurements was then used for statistical analysis.

Statistical Analysis

The same observer reviewed 20% of the images two weeks after the initial evaluation to increase the reliability of the assessments and the intra-observer correlation was found to be nearly perfect (κ: 0.92). All data have been analyzed using SPSS 29.0 (IBM Corp., New York) statistical software. The normality of the data was analyzed in accordance with the Kolmogorov-Smirnov test. The t-test was utilized to compare parametric data and the Mann-Whitney U test was utilized to compare nonparametric data. The statistical significant level was determined as $p<0.05$. Prior to commencing the study, G*power version 3.1.9.2 was used to determine the minimum number of patients required ($\alpha=0.05$, $1-\beta=0.95$).

RESULTS

The mean age of the pediatric patients aged 6-12 years (104 girls, 116 boys) participating in this study was 8.9±1.23 years.

The mean FD of the right condyle was 1.046±0.086 and the mean FD of the left condyle was 1.201±1.205 for the 9-12 age group, while the mean FD of the right condyle was 0.909±0.063 and the mean FD of the left condyle was 0.924±0.08 for the 6-8 age group. It was determined that mean FD values increased with age in both condyles, this rise was statistically significant ($p<0.001$) (Table 1).

When the mean FD values were analyzed according to gender, it was detected that the mean condyle FD value of boys was higher than that of girls (Table 2).

Table 1. Right and left condyle fractal dimension values between age groups

	9-12 age groups	6-8 age groups	p
Right condyle FD	1.046 ±0.086	0.909 ± 0.063	<0.001*
Left condyle FD	1.201±0.986	0.924±0.08	<0.001*

*p<0.05, FD: Fractal dimension

Table 2. Right and left condyle fractal dimension values between age groups in the same gender

		9-12 age groups (n=54)	6-8 age groups (n=62)	p
Boy	Right condyle FD	1.052±0.08	0.896±0.05	<0.001*
	Left condyle FD	1.364±1.71	0.925±0.09	<0.001*
		9-12 age groups (n=56)	**6-8 age groups (n=48)**	**p**
Girl	Right condyle FD	1.041±0.09	0.926±0.06	<0.001*
	Left condyle FD	1.045±0.09	0.944±0.09	<0.001*

*p<0.05, FD: Fractal dimension

In the same age group, there was not any significant difference between the mean FD values of the right and left condyles between genders ($p>0.05$). Additionally, though the mean FD of girls was higher than that of boys in the 6-8 age group and the mean FD of boys was higher than that of girls in the 9-12 age group, this difference is not considered to be significant (Table 3).

Table 3. Comparison of right and left condyle fractal dimension between genders in the same age group

	6-8 age groups		
	Girl (n=48)	**Boy (n=62)**	**p**
Right condyle FD	0.926±0.06	0.896±0.05	0.081
Left condyle FD	0.944±0.09	0.925±0.09	0.472
	9-12 age groups		
	Girl (n=56)	**Boy (n=54)**	**p**
Right condyle FD	1.041±0.09	1.052±0.08	0.629
Left condyle FD	1.045±0.09	1.364±1.71	0.724

*p<0.05, FD: Fractal dimension

DISCUSSION

The ability of the internal structure of viable bones to adapt to the mechanical forces to which it is exposed is one of its most critical features. The trabecular bone architecture is optimized for load-bearing function and the bone enlarges in reaction to the applied mechanical force. The assessment of alterations in bone structure depends on trabecular bone reliant on trabecular bone rather than than cortical bone due to its relatively higher metabolic activity.[8,17] Utilization of FA in radiographs is both trabecular analysis of bone microstructure as well as alveolar bone mineral content of the content.[18,19]

The impacts of many systemic diseases and dental anomalies on the jaw have been researched in the literature using the fractal method. Lower FD values have been correlated with lower bone density.[3,11,14,16,20] Hukuk et al.[21] compared four different methods and found that FA is a distinctive technique especially in the detection of bone changes. Magat et al.[23]

compared FA assessments in DPR, cone-beam computed tomography (CBCT) and recommended using DPRs for FA of trabecular bone due to the higher radiation dose and lower image resolution of CBCT. In FA method using box counting procedure, FD values are between 1 and 2.[13,24] Values closer to 1 represent simple structures with fewer fractals, while values closer to 2 indicate more complex bone structures. Nevertheless, there is no consensus in the literature that trabecular complexity increases as FD values increase. The differences in FD values can be attributed to anatomical variability, the application of different FA techniques and the selection of different jaw regions. In the literature, FD values in FA studies with DPRs of pediatric patients were found to be in the range of 0.62-1.44 on average.[3,11,14,16] There are also studies suggesting that FD increases with age.[25,26] This present study, considering the pediatric patient group, DPRs were used because of their advantages such as low radiation dose, easy applicability and routine use, and the most important finding of essential findings of the study was that the mean condyle FD values increased significantly with age.

In this study, that irradiation was carried out according as to age and weight of the children and the minimal technical differences in DPRs (kVp, exposure time) were insignificant for FA. However, Shourt et al.[26] reported that form and dimension of the ROI can affect the FA data of alveolar bone. In the study by Lee et al.[27] it was determined that linear ROI selection was insufficient to characterize the trabecular structure. Günacar et al.[28] chosen ROIs in the form of circles of 15x15 pixels. In the study by Bulut et al.[3] a 64x64 pixel square ROI was selected in the mandibular condyle. These square ROIs in the trabecular bone have been widely utilized in previous studies.[11,12,14,16] Several important regions of the mandible such as the antegonial notch, condyle and ramus undergo changes depending on age and growth development potential. Enlow et al. reported that the patient's age and dental condition have an effect on these remodeling regions.[24,25] In our study, square ROIs of 40 x40 pixels were used within the cortical borders of the mandibular condyle. However, there was no conclusive result on how this difference in ROI shapes affected the FD.

In previous studies, it has been concluded that the forces transmitted to the mandibular condyle and mandibular bone and the advance in bone consistency of these regions are affected by occlusal forces, the amount of teeth in the mouth and especially the presence of molar teeth.[29,30] Bulut et al.[3] analyzed the trabecular structures of the condyles with FA in the DPRs of 159 children aged 6-13 years and found that FD increased with age, but there was not found difference between right and left FDs except at the age of 6 years. In the current study, it is thought that the masticatory function of children in the 9-12 age group increases more with the change in the existing tooth structure compared to the 6-8 age group, and since bone development increases with age, the FD value is therefore higher in the 9-12 age group. Nevertheless, unlike Bulut et al.[3] there was a statistically significant difference between right and left condyle FDs in all age groups.

Guagnelli et al.[31] reported DXA trabecular bone scores of lumbar and hand bones in healthy childhood aged 4-19 years and resulted that gender showed a poor correlation with trabecular bone score. In their study Bulut et al.[3] found no significant difference between the condyle FDs of children and gender. Kolcakoglu et al.[16] investigated the trabecular bone formation in the mandible in pediatric patients diagnosed with sleep bruxism and in a control group using FA on panoramic radiographs and found that the FDs of patients with sleep bruxism were higher than those of the group without bruxism. However, no correlation was observed between FD values and age and gender. In this study, similar to the literature, there was found no significant difference between the mean FD values of the right and left condyles between the genders in the same age group.

The density of trabecular bone in children is an important factor in orthodontic treatment planning. It has been hypothesized that individuals with more dense trabecular structure may require higher forces to achieve tooth movement. Hence, individual differences in trabecular structure may affect the orthodontic treatment process and the magnitude of the applied force.[32] During orthodontic treatment, decreased bone density can lead to increased tooth movement speed, which may necessitate enhanced anchorage to maintain stability. Though this present study concentrated solely on the condylar region, previous literature emphasizes the importance of cortical bone structure in children for both orthodontic treatment planning and monitoring of growth and development. The density and distribution of the trabecular structure directly affects the efficiency of tooth movement, treatment duration and the magnitude of force required. For this reason, a broader assessment of bone structure may contribute to the development of more precise and individualized approaches for orthodontic and skeletal growth-related treatments.[32,33]

Limitations

Limitations of that study include the fact that the effect of both the preferred chewing place and the current dmft/DMFT status on the anatomy and bone compensation of condyles was not investigated. Furthermore, it has been shown that the mandibular condyle and trabecular structure are affected by changes in hormonal patterns during adolescence and tend to increase gradually with age. In addition, the limitation of the present study is that only the condyle was evaluated. In future studies, it is recommended to include the current dentition status of groups aged 13 years and older in order to evaluate the changes in FD values by examining not only the condyle but also other regions in the study with the effect of both the permanent dentition stage and hormonal changes during adolescence.

CONCLUSION

FA is considered a useful method for detecting and evaluating changes in bone structure. In conclusion, FA of DPR in this study showed that FD values of the trabecular structure of mandibular condyles of children aged 6-12 years improved with age however, there was no difference according to gender.

ETHICAL DECLARATIONS

Ethics Committee Approval

Prior to the study, ethics clearance was received from the Non-interventional Clinical Researches Ethics Board of Ankara Medipol University (Date: 06.06.2023, Decision No: 63).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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Original Article

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Preoperative and postoperative histologic grade in endometrial cancer: correlation with myometrial invasion

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ABSTRACT

Aims: Preoperative tumor histologic evaluation plays a crucial role in determining the surgical and therapeutic approach for endometrial cancer. However, discrepancies between preoperative and postoperative histopathological findings are common, potentially affecting clinical management.

Methods: This retrospective study included 287 patients diagnosed with endometrial cancer at Bakırköy Maternity and Children Training and Research Hospital. All patients underwent preoperative fractional dilatation and curettage (D&C) followed by total abdominal hysterectomy with or without lymphadenectomy. Preoperative and postoperative pathology reports were compared to assess concordance in tumor grade and histological subtype. The correlation between grade agreement and myometrial invasion was also analyzed.

Results: The histologic type changed in 17.6% of cases between preoperative curettage and postoperative hysterectomy. The tumor grade was upgraded in 50.7% of grade 1 cases and 11.6% of grade 2 cases. The overall concordance between the preoperative and postoperative tumor grading was weak (kappa=0.292, p<0.001). The grade agreement was higher in cases with deep myometrial invasion (kappa=0.32) than in those with superficial invasion (kappa=0.24).

Conclusion: The substantial rate of discordance between preoperative and postoperative histologic findings highlights the limitations of D&C in accurately predicting tumor grade. Given the impact of tumor grading on surgical and adjuvant treatment decisions, multimodal preoperative assessment integrating imaging and molecular profiling may improve diagnostic accuracy and optimize treatment strategies for endometrial cancer.

Keywords: Endometrial cancer, tumor grading, histologic concordance, myometrial invasion, dilatation and curettage

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in developed countries, with its incidence rising due to increasing life expectancy, obesity, and metabolic risk factors.[1] While it predominantly affects postmenopausal women, it can also occur in premenopausal patients with hereditary syndromes or hormone-related factors.[2] Effective management relies on preoperative histological assessment to guide treatment decisions and estimate prognosis.[3]

Preoperative evaluation, typically performed via endometrial biopsy or dilatation and curettage (D&C), helps differentiate endometrial carcinoma from benign conditions and identify aggressive histological subtypes. Endometrioid adenocarcinoma generally has a favorable prognosis, whereas non-endometrioid subtypes are associated with higher recurrence rates and poorer outcomes.[4]

Tumor grade, which reflects the differentiation status of cancer cells, is a key prognostic determinant of endometrial cancer.[5] High-grade tumors (grade 3) are more likely to exhibit deep myometrial invasion, lymphovascular space invasion, and metastasis, which necessitates aggressive surgical staging and adjuvant therapy. Accurate preoperative tumor grading is vital, as it guides decisions regarding the extent of surgery, including the necessity for lymphadenectomy and the choice between minimally invasive and open surgical techniques. In cases of high-grade disease, adjuvant chemotherapy and radiotherapy are frequently required even when other high-risk features are absent.[4,6]

This study systematically compares preoperative and postoperative tumor histology and grade in endometrial cancer patients. While previous research has suggested a correlation between tumor grade and myometrial invasion

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depth[8], the accuracy of preoperative grading in predicting myometrial invasion remains underexplored. By assessing the reliability of preoperative evaluations and identifying factors contributing to discrepancies, we aim to enhance diagnostic precision and optimize management strategies for endometrial cancer.

METHODS

This retrospective study was conducted as a graduation research project before 2020 in obstetrics and gynecology at Bakırköy Women and Children Training and Research Hospital (Thesis No: 10635735, Year: 2009). The study protocol was approved by the hospital's thesis approval committee and all research procedures were performed in accordance with the Declaration of Helsinki.

A total of 287 patients diagnosed with endometrial cancer through histopathological examination of hysterectomy specimens at the Gynecologic Oncology Clinic of Bakirköy Women and Children Training and Research Hospital were evaluated retrospectively. The study population included patients who had undergone preoperative fractional dilatation and curettage (D&C) for suspected endometrial pathology, received a confirmed postoperative diagnosis of endometrial cancer, and subsequently underwent hysterectomy with or without lymphadenectomy. Patients were excluded if they lacked a preoperative histopathological evaluation or had received preoperative chemotherapy or radiotherapy.

All patients underwent D&C as a diagnostic procedure before surgery. The surgical approach consisted of total abdominal hysterectomy (TAH) with or without bilateral salpingo-oophorectomy (BSO). When indicated, pelvic and/or para-aortic lymph node dissection was performed in accordance with the FIGO staging guidelines and based on the intraoperative findings. All surgeries were performed using an open surgical approach. At the time of this study, sentinel lymph node mapping had not yet been implemented as a standard procedure in our clinical practice for endometrial cancer management. Instead, systematic lymphadenectomy was performed based on preoperative and intraoperative risk assessments.

Pathological assessments were conducted in the hospital's pathology laboratory, where D&C and hysterectomy specimens were examined to determine the tumor histology, grade, and staging. Endometrial cancers were staged according to the FIGO staging system[10], and key clinicopathological variables were recorded, including patient demographics (age, menopausal status, comorbidities such as hypertension and diabetes mellitus), histopathologic subtype and grade, depth of myometrial invasion, presence of lymphovascular space invasion (LVSI), and lymph node involvement in cases where lymphadenectomy was performed. The results of preoperative (D&C) and postoperative (hysterectomy) pathology evaluations were systematically compared to assess histologic concordance and grade agreement, and the relationship between grade concordance and myometrial invasion depth was analyzed to identify potential correlations.

Statistical Analysis

All statistical analyses were conducted using SPSS for Windows (version 15.0). Descriptive statistics were used to summarize the data, including means, standard deviations, and frequency distributions. Intergroup differences were assessed using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical data. The weighted kappa test was employed to evaluate the degree of agreement between the preoperative and postoperative tumor grades, while multivariate logistic regression was performed to identify independent predictors of grade discordance. Statistical significance was set at $p<0.05$ analyses.

RESULTS

This study included 287 patients diagnosed with endometrial cancer. The mean age was 56.4 years (range: 33–80 years), with 15 patients (5.3%) aged ≤40 years. Of the total cohort, 85 patients (29.6%) were of reproductive age and 202 patients (70.4%) were postmenopausal. The most frequently reported clinical complaint was postmenopausal vaginal bleeding, observed in 73.1% of the cases.

Obesity (BMI >30 kg/m^2) was noted in 152 patients (53%), while 8 patients (2.8%) had a first-degree relative with a history of endometrial cancer. Hypertension was present in 93 patients (32.4%), diabetes in 11 patients (3.8%), and both conditions were documented in 33 patients (11.5%). Two patients (0.7%) had a history of tamoxifen use for breast cancer. The mean gravida and parity were 4.14 (range: 0–14) and 3.32 (range: 0–11), respectively. The median interval between endometrial sampling and surgical intervention was 25.38 days (range: 5–189 days).

Preoperative histopathological analysis of D&C samples identified endometrioid adenocarcinoma as the most frequent diagnosis in 229 patients (79.9%). Other notable diagnoses included serous papillary carcinoma in 20 cases (7.0%), atypical complex hyperplasia in 10 cases (3.5%), and various rare histological subtypes (Table 1). In 262 cases (91.3%), the preoperative diagnosis was confirmed as endometrial cancer, although 12 pathology reports did not specify tumor grade.

Tablo 1. Distribution of preoperative histopathologic diagnoses based on curettage material in the study population

Histopathologic diagnosis	n	%
Endometrioid adenocancer	229	79.9
Serous papillary carcinoma	20	7.0
Atypical complex hyperplasia	10	3.5
Clear cell carcinoma	8	2.8
Mucinous carcinoma	5	1.7
Endocervical adenocarcinoma	4	1.4
Atypical glandular hyperplasia	3	1.0
Simple atypical hyperplasia	2	0.7
Malignant mixed Müllerian tumor	2	0.7
Insufficient material	2	0.7
Atrophic endometrium	1	0.3
Endometrial polyp	1	0.3

Regarding surgical procedures, 20 patients (7%) underwent TAH+BSO alone, 131 (45.6%) underwent TAH + BSO + pelvic lymph node dissection (PLND), and 136 (47.4%) underwent TAH+BSO+Pelvic and para-aortic lymph node dissection (PPALND). Intraoperative frozen sections were performed in 18 patients (6.3%). Patients with grade 3 tumors in the preoperative D&C material were significantly more likely to undergo TAH+BSO+PPALND than other patients (p<0.01) (Table 2).

Postoperative histopathological examination of hysterectomy specimens revealed endometrioid adenocarcinoma as the predominant tumor type in 257 cases (89.6%), followed by serous papillary carcinoma in 26 cases (9.1%), clear cell carcinoma in one case (0.3%), and mucinous carcinoma in three cases (1.0%). The diagnosis of atypical endometrial hyperplasia in 15 cases was revised to endometrioid adenocarcinoma on postoperative examination. In total, 46 cases (17.6%) showed discrepancies between the preoperative and postoperative histological diagnoses (Table 3).

Tumor grade assessment showed an increase in grade in 69 patients (50.7%) initially diagnosed with grade 1 endometrial cancer and in 10 patients (11.6%) diagnosed with grade 2 endometrial cancer. The preoperative and postoperative tumor grade concordance rates were 49.3%, 69.8% for grade 2, and 50.0% for grade 1, 2, and 3 tumors, respectively. The overall agreement between the D&C and hysterectomy grades was weak but statistically significant (kappa=0.292, p=0.000) (Table 4).

Table 4. Comparison of tumor grade in curettage material with hysterectomy material

	Hysterectomy					
	Grade 1		Grade 2		Grade 3	
D&C	n	%	n	%	n	%
Grade 1	67	49.3	63	46.3	6	4.4
Grade 2	16	18.6	60	69.8	10	11.6
Grade 3	2	7.1	12	42.9	14	50.0

D&C: Dilatation curettage

Regarding myometrial invasion, 169 cases (58.9%) exhibited less than half myometrial invasion, 89 cases (31.0%) exhibited more than half invasion, and 29 cases (10.1%) showed no invasion.

Analysis of tumor grade concordance in relation to myometrial invasion demonstrated a weak but significant correlation in cases with less than half myometrial invasion (kappa=0.24, p=0.000). In cases with more than half myometrial invasion, the grade concordance was slightly improved (kappa=0.32). However, in cases without myometrial invasion, no significant correlation between the preoperative and postoperative tumor grades was observed (kappa=0.176, p=0.293) (Table 5).

DISCUSSION

This study aimed to evaluate the concordance between preoperative and postoperative tumor histology and grade in patients with endometrial cancer as well as its correlation with myometrial invasion. Our findings revealed a notable

Table 2. Operation performed according to the grade of the tumor in the curettage material

	Grade 1		Grade 2		Grade 3			
Surgical procedure	**n=136**	**%**	**n=86**	**%**	**n=28**	**%**	**Chi-square**	**p**
TAH+BSO	5	3.7	4	4.7	2	7.1		
TAH+BSO+PLND	79	58.1	31	36.0	7	25,0		
TAH+BSO+PPALN	52	38.2	51	59.3	19	67.9	16.187	.003

TAH+ BSO : Total abdominal hysterectomy and bilateral salpingo-oophorectomy, TAH+BSO+PLND: Total abdominal hysterectomy and bilateral salpingo-oophorectomy+pelvic lymph node dissection, TAH+BSO+PPALN: Total abdominal hysterectomy and bilateral salpingo-oophorectomy+ pelvic and paraaortic lymph node dissection

Table 3. Comparison of preoperative and postoperative histopathologic diagnosis

		Postoperative histopathologic diagnosis			
		Endometrioid adenocancer	**Serous papillary carcinoma**	**Clear cell carcinoma**	**Mucinous carcinoma**
Preoperative histopathologic diagnosis	Endometrioid adenocancer	210	15	1	3
	Serous papillary carcinoma	14	6	0	0
	Clear cell carcinoma	7	1	0	0
	Mucinous carcinoma	5	0	0	0
	Endocervical adenocarcinoma	2	2	0	0
	Simple atypical hyperplasia	2	0	0	0
	Atypical glandular hyperplasia	3	0	0	0
	Atypical complex hyperplasia	10	0	0	0
	Malignant mixed Müllerian tumor	1	1	0	0
	Insufficient material	1	1	0	0
	Endometrial polyp	1	0	0	0
	Atrophic endometrium	1	0	0	0

Table 5. A comparison of tumor grade in curettage material with hysterectomy material according to myometrial invasion

Myometrial invasion	D&C grade	Hysterectomy grade	n	%	Kappa	p-value
Less than half (<50%)	Grade 1	Grade 1	41	49.4	0.24	0.000
	Grade 1	Grade 2	38	45.8	0.24	0.000
	Grade 1	Grade 3	4	4.8	0.24	0.000
	Grade 2	Grade 1	12	21.4	0.24	0.000
	Grade 2	Grade 2	37	66.1	0.24	0.000
	Grade 2	Grade 3	7	12.5	0.24	0.000
	Grade 3	Grade 1	2	15.4	0.24	0.000
	Grade 3	Grade 2	6	46.2	0.24	0.000
	Grade 3	Grade 3	5	38.5	0.24	0.000
More than half (>50%)	Grade 1	Grade 1	9	28.1	0.32	0.000
	Grade 1	Grade 2	21	65.6	0.32	0.000
	Grade 1	Grade 3	2	6.3	0.32	0.000
	Grade 2	Grade 1	0	0	0.32	0.000
	Grade 2	Grade 2	22	88.0	0.32	0.000
	Grade 2	Grade 3	3	12.0	0.32	0.000
No invasion	Grade 1	Grade 1	17	81.0	0.176	0.293
	Grade 1	Grade 2	4	19.0	0.176	0.293
	Grade 1	Grade 3	0	0	0.176	0.293
	Grade 2	Grade 1	4	80.0	0.176	0.293
	Grade 2	Grade 2	1	20.0	0.176	0.293
	Grade 2	Grade 3	0	0	0.176	0.293
	Grade 3	Grade 1	0	0	0.176	0.293
	Grade 3	Grade 2	0	0	0.176	0.293
	Grade 3	Grade 3	1	1	0.176	0.293

D&C: Dilatation curettage

discrepancy between preoperative curettage and final hysterectomy pathology, particularly in cases of tumor grade and histologic subtype. These results align with those of previous studies that emphasized the limitations of preoperative sampling in accurately predicting the final tumor characteristics.[10,11]

Our study found that in 17.6% of cases, the histologic type changed between preoperative curettage and postoperative hysterectomy, indicating moderate inconsistency. This is in line with the prior literature, which reported discordance rates ranging from 10% to 30%.[7] Similarly, tumor grade upgrading was observed in 50.7% of grade 1 cases and 11.6% of grade 2 cases, reinforcing previous reports of grade misclassification due to the limited sampling area for curettage.[11]

A considerable proportion of tumors were found to have a higher grade on final pathology than that initially indicated by curettage specimens. The limitations of preoperative biopsy in capturing high-grade tumor foci have been previously highlighted by Vrede et al.[12], who found that increasing the amount of preoperative endometrial tissue sampled did not significantly improve concordance with the final tumor classification. This finding underscores the inherent challenges in accurately assessing tumor grade preoperatively, and suggests that factors beyond tissue volume, such as sampling bias and tumor heterogeneity, contribute to discordance.

Our weighted kappa value (0.292, p<0.001) suggests a weak agreement between the preoperative and postoperative grading, which is consistent with prior studies.[10]

The depth of myometrial invasion emerged as a crucial factor influencing grade concordance, with a higher concordance observed in tumors with deep myometrial invasion (kappa=0.32) than in those with superficial invasion (kappa=0.24). These findings underscore the importance of incorporating imaging modalities, such as magnetic resonance imaging (MRI), into preoperative assessments to improve accuracy in predicting tumor behavior.[11]

An important clinical implication of our findings is the potential for both overtreatment and undertreatment based on preoperative pathology alone. In our study, grade 3 tumors identified in curettage material were significantly associated with more extensive surgical interventions (p<0.01), aligning with the standard practice of performing pelvic and para-aortic lymphadenectomy in high-grade disease. However, in some cases where tumors were upgraded postoperatively, the initial surgical approach may have been insufficient, reinforcing the necessity of comprehensive preoperative assessment to optimize surgical planning.[11]

Compared with previous reports, our study supports the idea that D&C, despite being a widely used diagnostic tool, has inherent limitations in grading accuracy.[10]

Alternative approaches, such as hysteroscopic-guided biopsy and molecular profiling, may offer greater precision in predicting the final tumor characteristics and should be explored in future research.[11]

Previous studies have explored various factors influencing grading discrepancies, including tumor heterogeneity, sampling limitations, and interobserver variabilit. Recent research has also suggested that obesity-related factors, including body-mass index (BMI), may play a role in tumor grading variability. A higher BMI has been associated with differences in the tumor microenvironment and sampling limitations due to increased endometrial thickness, potentially contributing to grading discordance.[13] However our study did not include BMI as a variable and instead focused on histologic subtype and depth of myometrial invasion as key determinants of grading discrepancies.

Limitations

Our study has several strengths, including a large sample size (n=287) and systematic comparison of preoperative and postoperative histologic findings. However, this study has some limitations. First, its retrospective design introduced a potential selection bias. Second, the lack of routine use of advanced imaging techniques (such as MRI) may have influenced the assessment of myometrial invasion. Finally, interobserver variability in histological grading remains an inherent challenge in pathology.

CONCLUSION

Our findings highlight the substantial rate of discordance between preoperative and postoperative tumor histology and grade, reinforcing the need for cautious interpretation of preoperative biopsy results. Given the implications of tumor grade on surgical decision-making and adjuvant therapy selection, multimodal preoperative assessment—including advanced imaging and molecular profiling—should be considered to improve diagnostic precision. Future prospective studies integrating novel biomarkers and imaging modalities could enhance preoperative risk stratification and lead to more tailored treatment approaches in endometrial cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the thesis approval committee of Bakırköy Women and Children Training and Research Hospital (Thesis No: 10635735, Year: 2009).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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Original Article

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Epidemiological characteristics and anatomical distribution of glomus tumors: a single-center retrospective study

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ABSTRACT

Aims: Glomus tumors are rare, benign neoplasms arising from the glomus body, primarily found in the extremities. Although their clinical presentation is well-documented, their epidemiological characteristics and uncommon localizations remain subjects of ongoing research.

Methods: This retrospective study analyzed pathologically confirmed glomus tumor cases diagnosed at our institution between 2009 and 2025. Demographic data and anatomical localization were assessed.

Results: A total of 36 patients met the inclusion criteria, with a female predominance (n=19, 52.7%). The mean age at diagnosis was 48.97±14.31 years. Most tumors were located in the upper extremities (n=24, 66.7%), particularly in the digits, while 10 cases (27.8%) involved the lower extremities. Additionally, two rare cases were identified: one in the intergluteal region and another in the back. The fourth to sixth decades of life were the most commonly affected age range (77%).

Conclusion: Our findings align with previous literature regarding the prevalence of glomus tumors in the upper extremities and their higher occurrence in middle-aged individuals. However, rare localizations, such as the intergluteal region and back, highlight the need for a broader clinical perspective when diagnosing unexplained chronic pain. Future multicenter studies with larger cohorts may provide further insights into the epidemiology and clinical spectrum of glomus tumors.

Keywords: Glomus tumor, epidemiology, anatomical distribution, rare localizations

INTRODUCTION

Glomus bodies, small, specialized vascular structures found primarily in the skin, particularly in areas such as the fingertips, toes, ears, and nose.[1] These structures are involved in the regulation of blood flow and thermoregulation, playing a crucial role in maintaining body temperature by controlling the distribution of blood in response to environmental temperature changes.[2] Histologically, glomus bodies consist of arteriovenous anastomoses surrounded by specialized smooth muscle cells and endothelial cells, which allow them to regulate blood flow efficiently. The presence of specialized arteriolar blood vessels that can constrict or dilate in response to thermal stimuli is one of their distinctive features.[3]

Functionally, glomus bodies help protect the body from extreme temperature variations by constricting peripheral blood vessels in cold environments, thereby minimizing heat loss, and conversely, dilating these vessels in response to heat.[4] The importance of glomus bodies in thermoregulation is exemplified in regions of the body that are particularly vulnerable to temperature fluctuations, such as the extremities. Moreover, these structures are thought to play a role in sensory perception, particularly in detecting pain and cold stimuli.[4,5]

Despite their essential role in vascular and thermoregulatory functions, glomus bodies are also prone to abnormal growth, leading to the development of glomus tumors. Glomus tumors were first reported by Wood in 1812, and their histological characteristics were subsequently described by Barre and Mason in 1924.[6] Glomus tumors, though usually benign, arise from the hyperplasia of the smooth muscle and endothelial cells within the glomus body.[6,7] While this rare tumor usually localizes in the extremities, especially the upper extremities, it can also be present in visceral organs such as the lung, intestine and liver.[8]

The exact etiology behind this transformation remains incompletely understood; however, mutations in specific genes have been implicated in the pathogenesis of glomus tumors.[8] These tumors, typically presenting as painful lesions in the dermis, may cause significant discomfort and require surgical intervention. Love and cold sensitivity tests are used for diagnosis. In the Love test, which is commonly used during diagnostic evaluation, pain symptoms worsen when

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localized pressure is applied to the suspected area using a pointed object, such as the tip of a pen or a needle. Another diagnostic method involves assessing cold sensitivity; pain intensifies with exposure to cold and subsides when the area is warmed.[9] The gold standard treatment for glomus tumors is comlete surgical excision.[6]

Given the clinical significance of glomus tumors, understanding their epidemiological patterns is crucial for early diagnosis and effective management. This study aims to conduct a retrospective analysis of patients diagnosed with glomus tumors at our institution, with a focus on demographic characteristics such as patients' age, sex, and the anatomical localization of the tumors.

METHODS

The study was carried out with the permission of Giresun Training and Research Hospital Ethics Committee (Date: 07.02.2025, Decision No: 05.02.2025/07). This study was designed retrospectively. This study was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines, and other applicable laws and regulations. The word "glomus" was searched in pathology reports of the hospital information archive system retrospectively. The reports with diagnosed "glomus tm" were included to the study. The demographic data of patients' were noted. The age, sex, the excisional biopsy site, side if the site is on extremity.

RESULTS

Between 2009 to 2025, 36 patients met the inclusion criteria. Of the 36 patients' 19 were women and 17 were men with the mean age respectively (48.97±14.31, 48.5±12.01, 47.82±16.82). The range age were between 19-83 years. There were 19 left and 15 right side. In the remaining 2 patients, glomus tumors were located in the intergluteal region and back. The localizations of the glomuıs tumors are given in **Figure**.

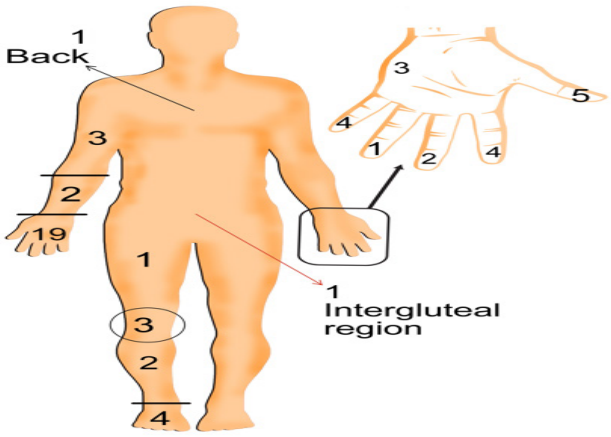

Figure. Anatomical localizations of glomus tumors and their frequency of occurrence

DISCUSSION

The epidemiological findings of pathologically diagnosed glomus tumors in our institution show both similarities and differences when compared to previously published studies. There are reports suggesting that glomus tumors can occur at any age with an equal distribution in young adults, while other studies indicate a higher prevalence in the fourth to sixth decades of life.[8,10] In our study, the majority of cases (77%) were diagnosed in patients within this fourth to sixth decades age range, aligning with the latter observation. In our study, glomus tumor was observed more frequently in women in accordance with the literatüre.[6,11]

A total of twenty-four cases were present at upper extremity and ten patients were present at lower extremity. In additon to the cases at extremites, one case was present at back and one case was prent at intergluteal region that was operated for piloniadal sinus. Regarding anatomical distribution, previous studies have reported that glomus tumors most commonly occur in the fingers of the hands and are more frequently found in the upper extremities compared to the lower extremities.[6,12] Similarly, our study demonstrated that the tumors were predominantly localized in the fingers, with a decreasing frequency observed in the upper and lower extremities.

Among the cases analyzed observed at hand, 84% of the glomus tumors were located in the digits, while 13% were found in the palm. This finding is in accordance with the data reported by Lin et al.[11], who found that 83% of 90 glomus tumors were located in the digits. Additionally, Jawalkar et al.[13] identified the index finger as the most commonly affected digit, followed by the middle finger, thumb, and ring finger. A study from Turkiye found the most affected fingers were index, thumb, middle finger, ring finger and little finger respectively.[14] In contrast, our study found that the thumb was the most frequently affected digit, followed by the little, index, middle, and ring fingers, suggesting that there may be some variability in the distribution of glomus tumors within the hand.

Glomus tumors occurring around the knee are rare, with only 37 cases reported in the literature.[15] Our study contributes three additional cases to this body of knowledge, further supporting the notion that glomus tumors should be considered in the differential diagnosis of periarticular pain.

Moreover, we identified a rare case of a glomus tumor localized in the back. Extradigital glomus tumors have been documented in the literature, including cases on the back, although they remain uncommon.[16] This finding underscores the importance of maintaining clinical suspicion for glomus tumors in atypical locations, particularly in patients with chronic, unexplained pain.

The other rare presentation of the glomus tumor in our cohort was presented at pilonoidal sinus. Glomus tumours may be considered in the differential diagnosis of pilonoidal sinus in a patient presenting with tenderness in the intergluteal region.[17]

The studies demonstrating the anatomical localizations of glomus tumors are rare.[8] According to the literature search, studies from Türkiye typically focus on specific systems, such as the musculoskeletal system, head and neck surgery, and the gastrointestinal system.[18-20] No study from Turkey has been found in the literature that investigates the anatomical localizations of glomus tumors. In this context, the current

study may be the first from Turkiye to examine the anatomical localizations of glomus tumors.

Limitations

This study has several limitations. First, the retrospective nature of our analysis may have led to selection bias, as only pathologically confirmed cases were included. Additionally, the relatively small sample size limits the generalizability of our findings. Our study was conducted at a single institution, which may not fully represent the epidemiological distribution of glomus tumors in broader populations.

CONCLUSION

In conclusion, our findings largely corroborate existing literature regarding the demographic and anatomical distribution of glomus tumors, while also contributing new data on less common tumor localizations. Future studies with larger sample sizes and multicenter data collection may provide further insights into the epidemiology and clinical presentation of this rare neoplasm.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Giresun Training and Research Hospital Ethics Committee (Date: 07.02.2025, Decision No: 05.02.2025/07).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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Original Article

MEDICINE PALLIATIVE CARE

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Evaluation of risk factors contributing to device-related pressure ulcer development in critically ill patients*

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ABSTRACT

Aims: Device-related pressure ulcers are one of the most common complications observed in patients treated in intensive care units (ICUs). These ulcers negatively impact patient comfort and significantly increase treatment costs. To prevent and manage pressure ulcers caused by medical devices, it is essential to thoroughly understand the associated risk factors. This study aims to determine the prevalence of device-related pressure ulcers in critically ill patients and evaluate the risk factors contributing to their development.

Methods: The study included 91 patients who were monitored with non-invasive mechanical ventilation (NIMV) in the pulmonary intensive care unit between January 1, 2021, and December 31, 2021. The patients' demographic characteristics, nutritional status, body-mass index (BMI), biochemical parameters, and Braden pressure ulcer risk assessment scale scores of the patients were retrospectively analyzed.

Results: The findings revealed no direct relationship between the duration of medical device use and the development of pressure ulcers. However, an increase in the number of days masks were used was significantly associated with the progression of pressure ulcer stages, particularly from early to advanced stages. The study also found that the Braden scoring system was insufficient in predicting pressure ulcers caused by oronasal masks, while patients with higher blood urea nitrogen (BUN) levels tended to have ulcers that remained at early stages without progression. No significant association was found between pressure ulcer development and nutritional status, albumin levels, BMI, or corticosteroid use. However, prolonged ICU stays were associated with the progression of pressure ulcers to more advanced stages.

Conclusion: These results emphasize the importance of optimizing the duration of device usage and selecting appropriate devices to prevent device-related pressure ulcers.

Keywords: Device-related pressure ulcer, non-invasive mechanical ventilation, Braden score, intensive care unit, risk factors

*A limited portion of the data from this study was presented as an oral presentation at the 2nd International Congress on Medicine, Health, and Communication Sciences (October 5-8, 2022).

INTRODUCTION

Pressure ulcers are defined as ischemia, cell death, and tissue necrosis that develop due to prolonged pressure on tissues, typically occurring over areas of bony prominences. Pressure ulcers not only significantly increase treatment and hospitalization costs for inpatients but also greatly reduce patient comfort.[1] Standardizing the diagnosis and staging of pressure ulcers is crucial for treatment monitoring. To this end, staging systems, often recommended by the National pressure injury advisory panel, are commonly used.[2]

The development of pressure ulcers is influenced by certain intrinsic factors related to the patient. Advanced age, smoking, the presence of systemic diseases (such as pulmonary disease, heart disease, diabetes, renal disease), cognitive impairment, high fever, and severe spasticity are all factors that facilitate the development of pressure ulcers.[3] Malnutrition is also recognized as a predisposing factor. Most pressure ulcers are associated with hypoalbuminemia (<3.5 g/dl) due to insufficient nutritional intake. When serum albumin levels fall below 3.5 g/dl, the prevalence of pressure ulcers is approximately 75%, whereas this prevalence drops to 16% when albumin levels exceed this threshold. Additionally, anemia, hypercholesterolemia, dehydration, and deficiencies in ascorbic acid, zinc, calcium, magnesium, vitamin D, and

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vitamin E are other nutritional risk factors for pressure ulcer development.[4]

Moisture caused by incontinence or sweating facilitates skin maceration, making tissues subjected to pressure more prone to necrosis.[5] To assess the risk of pressure ulcer development in intensive care units (ICUs), evaluation scales such as the Braden, Waterlow, and Norton are utilized, with the Braden scale being the most widely used. Studies have shown that patients classified as high-risk according to the Braden scale are more likely to develop pressure ulcers.[6]

Device-related pressure ulcers, which are a core component of diagnosis and treatment, differ from traditional pressure ulcers.[7] In device-related pressure ulcers, lesions typically appear on the skin or mucosa rather than over bony prominences.[8] On the other hand, traditional pressure ulcers usually occur over bony areas and/or tissues exposed to pressure due to immobility or inadequate support surfaces. Device-related pressure ulcers often depend on the position and shape of the medical device. However, the risk factors for both types are similar. Considering the frequent use of medical devices in ICU patients, the risk of pressure ulcers in this group inevitably increases.

In conclusion, there is no ideal or universal method for the prevention and treatment of pressure ulcers. Nevertheless, avoiding risk factors, implementing preventive measures, using support surfaces, applying appropriate dressings, and utilizing specific physical therapy techniques provide physicians and nurses with effective and economical approaches tailored to the patients' needs. Therefore, it is crucial to take the necessary precautions for patients at high risk of developing pressure ulcers and to develop cost-effective and efficient treatment methods after ulcer formation.

In this study, we aim to identify the prevalence of pressure ulcers associated with the use of medical devices (such as BIPAP, CPAP, etc.) in a pulmonary ICU and to highlight related risk factors. In parallel, we intend to discuss potential measures to reduce the incidence of pressure ulcers during subsequent patient follow-ups.

METHODS

Our study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, and approval was obtained from the Clinical Researches Ethics Committee of the University of Health Sciences, Ankara Keçiören Training and Research Hospital (Date: 25.01.2022, Decision No: 2012-KAEK-15/2467). Patients meeting the inclusion and exclusion criteria outlined in the study protocol were retrospectively reviewed and analyzed.

The study included patients who were followed for at least three[3] days on non-invasive mechanical ventilation (NIMV) between January 1, 2021, and December 31, 2021, in the pulmonary intensive care unit of our hospital. In addition to the patients' demographic data, the following parameters were evaluated and recorded: pressure ulcers associated with medical devices (oronasal or nasal masks), comorbidities, duration of device use, body-mass index (BMI), nutritional status, corticosteroid use, and serum biochemical values including blood urea nitrogen (BUN), creatinine, albumin, total protein, sodium, potassium, calcium, magnesium, uric acid, glucose levels, as well as hemogram parameters such as hemoglobin and white blood cell counts.

The Braden pressure ulcer risk assessment scores recorded within the first three days of the patients' ICU admission were collected. Malnutrition risk status was assessed using the Nutritional Risk Screening-2002 (NRS-2002). Over a total follow-up period of 18 days, device-related pressure ulcers and their stages were recorded.

The relationships between pressure ulcers, including their stages, and patients' biochemical and hemogram data, Braden pressure ulcer risk assessment scores, total duration of device use, and nutritional status were analyzed.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Patients aged 18 years or older.
- Patients monitored with an oronasal mask for NIMV for at least 9 days.

Exclusion criteria:

- Patients younger than 18 years.
- Patients who used a mask for NIMV for less than three days.
- Patients who died within the first 9 days of hospitalization.
- Patients discharged before 9 days.
- Patients who did not sign the informed consent form.

Use of Oro-Nasal Masks in Patients

In our clinic, NIMV devices are utilized for patients with type 2 respiratory failure. When using these devices, oro-nasal masks are preferred as the first choice to minimize anatomical dead space, enhance patient compliance, and prevent feelings of claustrophobia. While nasal masks are unsuitable for patients who predominantly breathe through their mouths, full-face masks are not preferred as the first choice in our clinic due to their tendency to increase both anatomical dead space and claustrophobic sensations.

To enhance the effectiveness of NIMV and maintain leakage rates below 50%, specific measures are implemented when applying oro-nasal masks. These include shaving beards in male patients before mask application, ensuring that gastric tubes in patients with nasogastric tubes remain clamped within the mask, and securing the mask straps with adequate tightness. These precautions were applied to all patients included in the study.

Braden Pressure Ulcer Risk Assessment Scale

The Braden pressure ulcer risk assessment scale, developed by Braden and Bergstrom[9], underwent its first reliability and validity study in Turkey by Oğuz in 1997. In 1998, Pınar and Oğuz[10] further examined the reliability and validity of the Norton and Braden Risk Assessment Scales, finding both to have high reliability and validity.

The scale consists of six subscales: sensory perception, moisture, activity, mobility, nutrition, and friction/shear. The total score, ranging from 6 to 23, is obtained by summing the scores of the subscales (Table 1). Based on the total score:

- A score of 12 or lower indicates a high risk.
- A score of 13–14 indicates a moderate risk.
- A score of 15–16 indicates a low risk.
- For individuals over 75 years of age, a score of 15–18 is also considered a low risk.[11]

Statistical Analysis

IBM SPSS (Statistical Package for the Social Sciences) Statistics, Version 27 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Categorical (nominal) data were presented as n (%) values. Ordinal data or numerical data that did not follow normal distribution were presented as median (min-max), whereas numerical data that followed a normal distribution were presented as mean (SD).

For categorical variables, the chi-square test was used if each cell had more than five cases. If at least one cell had fewer than five cases, Fisher's exact test was applied. For comparisons of categorical variables with more than two categories, the likelihood ratio test was employed when at least one cell contained fewer than five cases in the cross-tabulation.

Numerical data were analyzed using the Student's t-test if they exhibited a normal distribution, and the Mann-Whitney U test if they did not. For comparisons involving numerical variables with more than two categories, one-way ANOVA was used for normally distributed data, and the Kruskal-Wallis H test was applied for non-normally distributed data.

The normality of numerical data was assessed using descriptive statistics, including Kolmogorov-Smirnov and Shapiro-Wilk tests, skewness-kurtosis values, histograms, and an evaluation of the proximity of outliers. If a significant difference was observed between group means for normally distributed numerical variables, effect size was calculated using Cohen's d value.

A 95% confidence interval was used for all analyses, and statistical significance was set at $p<0.05$.

RESULTS

The data from a total of 91 patients meeting the inclusion criteria of the study were analyzed. The mean age of the patients was calculated to be 66.8±8 years. Of the patients, 62.6% (n=57) were male, and 37.4% (n=34) were female.

Pressure ulcers caused by the use of oronasal masks for NIMV were classified based on their severity on the third, sixth, and ninth days of hospitalization as follows:

- **Stage 0:** No ulcer.
- **Stage 1:** Redness.
- **Stage 2:** Disruption of skin integrity.
- **Stage 3:** Ulcer involving all layers of the skin.
- **Stage 4:** Ulcer causing tissue loss.

Additionally, Braden pressure ulcer risk scores were recorded for all patients within the first three days of hospitalization. Nutritional status was assessed using NRS-2002 scores at the time of admission. All other variables mentioned in the "materials and methods" section were also analyzed.

PRESSURE ULCER STATUS ON DAY 3

At this stage of the study, 10 out of 91 patients (10.9%) had not yet developed device-related pressure ulcers, while 81 out of 91 patients (89.1%) had developed stage 1 pressure ulcers.

No significant differences were found between the groups with and without pressure ulcers in terms of the following parameters measured at ICU admission: hemoglobin, hematocrit, albumin, sodium, potassium, calcium, glucose, white blood cell count, neutrophil count, creatinine, BUN, and uric acid levels.

Similarly, there were no significant differences between the two groups regarding BMI, the number of days corticosteroids were used, total corticosteroid dosage, daily corticosteroid dosage, the number of hours masks were used daily, or the total number of days masks were used (Table 2).

Additionally, no significant differences were observed between the groups with and without pressure ulcers on the third day in terms of the presence of diabetes mellitus (DM), hypertension (HT), heart failure, or pneumonia. No significant associations were found based on gender, ICU admission source, or Braden risk score categories (Table 2).

Pressure Ulcer Status on Day 6

By the sixth day of the study, 8 out of 91 patients (8.7%) had not developed pressure ulcers, while 62 out of 91 patients (68.2%) had stage 1 pressure ulcers and 21 out of 91 patients (23.1%) had stage 2 pressure ulcers.

The results of one-way ANOVA and Kruskal-Wallis H tests showed no significant differences among these three groups (no ulcer, stage 1, and stage 2) in terms of hemoglobin, hematocrit,

Table 1. Braden pressure ulcer risk assessment scale

Subparameters	Point: 1	Point: 2	Point: 3	Point :4
Sensory perception	Completely limited	Very limited	Slightly limited	No impairment
Moisture	Constantly moist	Very moist	Occasionally moist	Rarely moist
Aktivity	Bedbound	Chairbound	Walk occasionaly	Walks frequently
Mobility	Completely immobile	Very limited	Slightly limited	No limitations
Nutrition	Very poor	Probably inadequate	Adequate	Excellent
Friction and shear	Problem	Potential problem	No apparent problem	No problem

Table 2. Analysis of data according to device-related pressure ulcer status on the third day

Variable	Pressure ulcer non-developing group mean±sd, median (min-max), n (%)				Pressure sore developing (Stage 1) mean±sd, median (min-max), n (%)				p value
Hemoglobin (g/dl)	13.76±2.25				13.30±2.45				0.577[a]
Hematocrit (%)	45.76±8.51				43.10±8.06				0.331[a]
Glucose (mg/dl)	133.5 (72.0–285.0)				136.0 (72.0–675.0)				0.934[b]
WBC (/µl)	8550 (4670–11070)				9350 (2930–38560)				0.542[b]
Creatinine (mg/dl)	1.14 (0.53–1.75)				0.87 (0.08–1.8)				0.238[b]
BUN (mg/dl)	30.0 (9.0–49.0)				22.0 (8.0–65.0)				0.064[b]
Uric acid (mg/dl)	7.05 (5.5–12.0)				5.6 (2.0–18.07)				0.050[b]
Albumin (g/dl)	3.38±0.44				3.42±0.45				0.771[a]
Sodium (mmol/l)	141.0±4.47				139.08±4.99				0.281[a]
Calcium (mg/dl)	9.01±0.78				8.83±0.58				0.382[a]
Potassium (mmol/l)	4.67±0.82				4.56±0.56				0.599[a]
Number of mask days	10.0 (3.0–11.0)				8.0 (3.0–34.0)				0.899[b]
Daily mask duration	10.0 (6.0–12.0)				10.0 (4.0–22.0)				0.119[b]
Steroid daily dose (methylprednisolone) (mg)	0.0 (0.0–40.0)				26.0 (0.0–135.0)				0.402[b]
Total steroid dose (methylprednisolone) (mg)	0.0 (0.0–320.0)				80.0 (0.0–960.0)				0.462[b]
Number of days steroid applied	0.0 (0.0–9.0)				2.0 (0.0–30.0)				0.482[b]
BMI (kg/m^2)	26.7 (20.44–37.11)				26.12 (15.94–67.75)				0.643[b]
NRS-2002	3.5 (3.0–5.0)				4.0 (3.0–7.0)				0.463[b]
Braden score	20 (10-22)				18 (10-22)				0.282[b]
DM	Yes: 2 (20%)		No: 8 (80%)		Yes: 23 (28.4%)		No: 58 (71.6%)		0.721[c]
HT	Yes: 2 (20%)		No: 8 (80%)		Yes: 13 (16%)		No: 68 (84%)		0.667[c]
Heart failure	Yes: 1 (10%)		No: 9 (90%)		Yes: 5 (6.2%)		No: 76 (93.8%)		0.513[c]
Gender	Male: 4 (40%)		Female: 6 (60%)		Male: 53 (65.4%)		Female: 28 (34.6%)		0.166[c]
Pneumonia	Yes: 0 (0%)		No: 10 (100%)		Yes: 11 (13.6%)		No: 70 (86.4%)		0.603[c]
Place of admission to ICU	Emergency sevice: 7 (70%)	Other department: 1 (10%)	Other ICU: 2 (20%)		Emergency sevice: 45 (55.6%)	Other department: 13 (16%)	Other ICU: 23 (28.4%)		0.672[d]
Braden risk category	A: 6 (60%)	B: 3 (30%)	C: 0 (0%)	D: 1 (10%)	A: 36 (44.4%)	B: 36 (44.4%)	C: 4 (4.9%)	D: 5 (6.2%)	0.569[d]

a Student t test, b Mann-Whitney U testi, c Fisher exact, d Likelihood ratio, BUN: Blood urea nitrogen, DM: Diabetes mellitus, HT: Hypertension, ICU: Intensive care unit, NRS: Nutritional risk score, BMI: Body-mass index, YB: Intensive care, A: Risk-free, B: Low risk, C: Risky, D: High risk

albumin, sodium, potassium, calcium, glucose, white blood cell count, creatinine, uric acid, and neutrophil levels (Table 3). Similarly, there were no significant differences in BMI, the number of days corticosteroids were used, total corticosteroid dosage, daily corticosteroid dosage, the number of hours masks were used daily, Braden scores (both at admission and the sixth day), or NRS-2002 scores among the groups.

Significant Findings

BUN levels: A significant difference in BUN values was observed among the three groups (p=0.033). Pairwise comparisons revealed that patients without ulcers had significantly higher BUN levels compared to those with stage 1 ulcers (p=0.018). However, no significant difference was found in BUN values between patients with stage 1 and stage 2 ulcers (Table 3).

Duration of mask use: A significant difference was also identified in the number of days masks were used among the groups (p=0.021). Pairwise comparisons showed no significant difference between patients without ulcers and those with stage 1 ulcers. However, patients with stage 2 ulcers had a significantly longer duration of mask use compared to those with stage 1 ulcers (p=0.006) (Table 3).

Other Findings

No significant differences were found among the groups in terms of the presence of DM, HT, or pneumonia. Additionally, there were no significant associations based on gender, ICU admission source, or Braden risk score categories (Table 3).

Pressure Ulcer Status on Day 9

By the ninth day of the study, the distribution of patients across pressure ulcer stages was as follows:

- No ulcer**:** 8 patients (8.7%).
- Stage 1: 58 patients (63.7%).
- Stage 2**:** 22 patients (24.1%).
- Stage 3**:** 3 patients (3.2%).

Table 3. Analysis of data according to device-related pressure ulcer status on the sixth day

Variable	Pressure ulcer non-developing group mean±SD, median (min-max), n (%)	Pressure sore developing (stage 1) mean±SD, median (min-max), n (%)	Pressure sore developing (stage 2) mean±SD, median (min-max), n (%)	p value
Hemoglobin (g/dl)	13.3±0.7	13.2±0.3	13.7±0.4	0.683[e]
Hematocrit (%)	43.9±2.1	42.6±1.1	45.4±1.4	0.397[e]
Glucose (mg/dl)	148 (102-285)	132 (72-418)	138 (79-675)	0.628[f]
WBC (/µl)	9140 (4670-11070)	9175 (2930-38560)	9950 (6740-17460)	0.302[f]
Serum creatinine (mg/dl)	1.21 (0.69-1.75)	0.84 (0.8-1.8)	0.92 (0.57-1.47)	0.096[f]
BUN (mg/dl)	32 (19-49)	22.5 (8-65)	18 (13-38)	**0.033**[f*]
Uric acid (mg/dl)	6.9 (5.5-12)	5.6 (2-18.07)	6.1 (2.3-11.7)	0.186[f]
Albumin (g/dl)	3.3±0.11	3.4±0.05	3.49±0.1	0.718[e]
Sodium (mmol/l)	140.6±1.7	139±0.66	139.5±0.94	0.669[e]
Calcium (mg/dl)	8.9±0.16	8.8±0.07	8.7±0.13	0.492[e]
Potassium (mmol/l)	4.6±0.22	4.4±0.07	4.7±0.11	0.183[e]
Number of mask days	10 (3-11)	7 (3-34)	9 (7-30)	0.021[f]
Daily mask duration	10 (6-12)	10 (6-22)	10 (4-16)	0.902[f]
Steroid daily dose (methylprednisolone) (mg)	0 (0-40)	28 (0-125)	0 (0-135)	0.126[f]
Total steroid dose (methylprednisolone) (mg)	0 (0-320)	80 (0-960)	0 (0-540)	0.796[f]
Number of days steroid applied	0 (0-9)	3 (0-30)	0 (0-17)	0.915[f]
BMI (kg/m^2)	26.4 (20.4-37.1)	26.1 (15.9-67.7)	26.1 (17.7-41.9)	0.991[f]
NRS-2002	3 (3-5)	4 (3-7)	4 (3-6)	0.348[f]
Braden score	20 (10-22)	18 (10-22)	17(12-22)	0.563[f]
DM	Yes: 2 (25%) / No: 6 (75%)	Yes: 19 (30.6%) / No:43 (69.4%)	Yes: 4 (19%) / No: 17 (81%)	0.566[d]
HT	Yes: 2 (25%) / No: 6 (75%)	Yes: 7 (11.3%) / No: 55 (88.7%)	Yes: 6 (28.6%) / No: 15 (71.4%)	0.163[d]
Heart failure	Yes: 1 (12.5%) / No: 7 (87.5%)	Yes: 4 (6.5%) / No: 58 (93.5%)	Yes: 1 (4.8%) / No: 20 (95.2%)	0.782[d]
Gender	Female: 4 (50%) / Male: 4 (50%)	Female: 23 (37.1%) / Male: 39 (62.9%)	Female: 7 (33.3%) / Male:14 (66.7%)	0.712[d]
Pneumonia	Yes :0 (0%) / None: 8 (100%)	Yes: 7 (11.3%) / None: 55 (88.7%)	Yes: 4 (19%) / None: 17 (83%)	0.231[d]
Place of admission to ICU	Emergency service : 5 (62.5%) / Other department: 1 (12.5%) / Other ICU: 2 (25%)	Emergency service: 37 (59.7%) / Other department: 9 (14.5%) / Other ICU: 16 (25.8%)	Emergency service: 10 (47.6%) / Other department: 4 (19%) / Other ICU: 7 (33.3%)	0.904[d]
Braden risk category	A: 5(62.5%) / B: 2 (25%) / C: 0 (0%) / D: 1 (12.5%)	A: 27 (43.5%) / B: 31 (50%) / C: 1 (1.6%) / D: 3(4.8%)	A: 10 (47.6%) / B: 6 (28.6%) / C: 3 (14.3%) / D: 2(9.5%)	0.173[d]

d Likelihood ratio, e One way anova, f Kruskal-Wallis H test, SD: Standard deviation, BUN: Blood urea nitrogen, DM: Diabetes mellitus, HT: Hypertension, ICU: Intensive care unit, NRS: Nutritional Risk Score, BMI: Body-mass index, A: Risk-free, B: Low risk, C: Risky, D: High risk

Statistical analysis using one-way ANOVA and Kruskal-Wallis H tests revealed no significant differences among these four groups in terms of hemoglobin, hematocrit, albumin, sodium, potassium, calcium, glucose, white blood cell count, creatinine, uric acid, BUN, and neutrophil levels (Table 4). Similarly, no significant differences were observed for BMI, the number of days corticosteroids were used, total corticosteroid dosage, daily corticosteroid dosage, the number of hours masks were used daily, Braden scores, Braden scores measured on the ninth day, or NRS-2002 scores among the groups (Table 4).

Significant Findings

Duration of mask use: A significant difference was observed in the number of days masks were used among the groups (p=0.003). Pairwise comparisons: No significant difference was found between patients without ulcers and those with stage 1 ulcers. Patients with stage 2 ulcers had a significantly longer duration of mask use compared to those with stage 1 ulcers (p=0.001). While patients with stage 3 ulcers had a longer duration of mask use than those with stage 2 ulcers, this difference was not statistically significant.

Length of ICU stay: A significant difference was also found in the length of ICU stay among the groups (p=0.016).

Pairwise comparisons: No significant difference was found between patients without ulcers and those with stage 1 ulcers, or between stage 1 and stage 2 ulcer groups. However, patients with stage 3 ulcers had a significantly longer ICU stay compared to those with stage 2 ulcers (p=0.027).

Table 4. Analysis of data according to device-related pressure ulcer status on the ninth day

Variable	Pressure ulcer non-developing group mean±SD, median (min-max), n (%)	Pressure sore developing (stage 1) mean±SD, median (min-max), n (%)	Pressure sore developing (stage 2) mean±SD, median (min-max), n (%)	Pressure sore developing (stage 3) mean±SD, median (min-max), n (%)	p value
Hemoglobin (g/dl)	13.3±0.7	13.1±0.3	13.7±0.4	15.2±1.5	0.412[e]
Hematocrit (%)	43.9±2.1	42.4±1.1	44.8±1.3	49.9±4.5	0.319[e]
Glucose (mg/dl)	148 (102-285)	132 (72-418)	138 (79-675)	92 (88-127)	0.260[f]
WBC (/µl)	9140 (4670-11070)	9175 (2930-38560)	9820 (5540-19380)	9270 (6780-12580)	0.598[f]
Serum creatinine (mg/dl)	1.2 (0.69-1.75)	0.83 (0.8-1.8)	0.93 (0.58-1.65)	0.8 (0.57-1)	0.114[f]
BUN (mg/dl)	32 (19-49)	22 (8-58)	20 (13-65)	20 (18-26)	0.087[f]
Uric acid (mg/dl)	6.9 (5.5-12)	5.6 (2-11.9)	6.1 (2.3-18.7)	4.8 (4.7-11.7)	0.332[f]
Albumin (g/dl)	3.3±0.11	3.3±0.05	3.5±0.1	3.4±0.2	0.736[e]
Sodium (mmol/l)	140.6±1.7	139±0.6	139.3±1	139.6±1.7	0.873[e]
Calcium (mg/dl)	8.9±0.1	8.8±0.08	8.7±0.12	8.5±0.13	0.584[e]
Potassium (mmol/l)	4.6±0.2	4.4±0.07	4.7±0.11	4.3±0.3	0.227[e]
Number of mask days	10 (3-11)	7 (3-34)	9 (7-30)	15 (14-15)	***0.003***[f*]
Daily mask duration	10 (6-12)	10 (6-22)	10 (4-16)	12 (10-12)	0.292[f]
Steroid daily dose (methylprednisolone) (mg)	0 (0-40)	28 (0-125)	0 (0-135)	28 (0-31)	0.192[f]
Total steroid dose (methylprednisolone) (mg)	0 (0-320)	80 (0-960)	0 (80-540)	200 (0-380)	0.536[f]
Number of days steroid applied	0 (0-9)	3 (0-30)	0 (0-17)	7 (0-12)	0.648[f]
BMI (kg/m^2)	26.4 (20.4-37.1)	25.8 (16.6-67.7)	26.8 (15.9-54.6)	24.4 (22.9-29.1)	0.928[f]
NRS-2002	3 (3-5)	4 (3-7)	4 (3-6)	4 (4-4)	0.619[f]
Braden score	20 (10-22)	18 (10-22)	18 (12-22)	16 (12-21)	0.679[f]
DM	Yes: 2 (25%) / No: 6 (75%)	Yes: 19 (32.8%) / No: 39 (67.2%)	Yes: 4 (18.2%) / No: 18 (581.8)	Yes: 0 (0%) / No: 3 (100%)	0.287[d]
HT	Yes: 2 (25%) / No: 6 (75%)	Yes: 5 (8.6%) / No: 53 (91.4%)	Yes: 7 (31.8%) / No: 15 (68.2%)	Yes: 1 (33.3%) / No: 2 (66.7%)	0.07[d]
Heart failure	Yes: 1 (12.5%) / No: 7 (87.5%)	Yes: 3 (5.2%) / No: 55 (94.8%)	Yes: 2 (9.1%) / No: 20 (90.9%)	Yes: 0 (0%) / No: 3 (100%)	0.758[d]
Gender	Female: 4 (50%) / Male: 4 (50%)	Female: 22 (37.9%) / Male: 36 (62.1%)	Female: 7 (31.8%) / Male: 15 (68.2%)	Female: 1 (33.3%) / Male: 2 (66.7%)	0.837[d]
Pneumonia	Yes: 0 (0%) / No: 8 (100%)	Yes: 7 (12.1%) / No: 51 (87.9%)	Yes :4 (18.2%) / No: 18 (81.8%)	Yes: 0 (0%) / No: 3 (100%)	0.319[d]
Place of Admission to ICU	Emergency service: 5 (62.5%) / Other department: 1 (12.5%) / Other ICU: 2 (25%)	Emergency service: 35 (60.3%) / Other department: 8 (13.8%) / Other ICU: 15 (25.9%)	Emergency service: 10 (45.5%) / Other department: 5 (22.7%) / Other ICU: 7 (31.8%)	Emergency service: 2 (66.7%) / Other department: 0 (0%) / Other ICU: 1 (33.3%)	0.840[d]
Braden risk category	A: 5 (62.5%) / B: 2 (25%) / C: 0 (0%) / D: 1 (12.5%)	A: 26 (44.8%) / B: 28 (48.3%) / C: 1 (1.7%) / D: 3 (5.2%)	A: 10 (45.5%) / B: 8 (36.4%) / C: 3 (13.6%) / D: 1 (4.5%)	A: 1 (33.3%) / B: 1 (33.3%) / C: 0 (0%) / D: 1 (33.3%)	0.421[d]

d Likelihood ratio, e One way anova, f Kruskal-Wallis H testi, SD: Standard deviation, BUN: Blood urea nitrogen, DM: Diabetes mellitus, HT: Hypertension, ICU: Intensive care unit, NRS: Nutritional Risk Score, BMI: Body-mass index, A: Risk-free, B: Low risk, C: Risky, D: High risk

Other Findings

No significant differences were observed among the groups in terms of the presence of DM, HT, or pneumonia. Additionally, no significant associations were found based on gender, ICU admission source, or Braden risk score categories (Table 4).

DISCUSSION

In this study, we aimed to analyze the development of pressure ulcers caused by oronasal masks used for NIMV in respiratory ICUs. We evaluated this in relation to variables such as patients' nutritional and inflammatory status (as reflected by admission blood values), BMI, the use of corticosteroids (commonly administered in respiratory ICUs), and the presence of certain clinical conditions, which we hypothesized could influence the development of pressure ulcers on the nose and surrounding tissues.

The predictive value of pressure ulcer risk assessment tools in bedridden patients has been demonstrated in previous studies.[6,12] However, no studies were found in the literature that specifically evaluated the effectiveness of oronasal masks used for NIMV in predicting pressure ulcer development. A multicenter study conducted in Iran reported that low Braden risk score averages for nasal oxygen tubes, oxygen face masks, and endotracheal tubes were significantly associated with an increased risk of ulcer development.[13] In our study, we compared Braden scores both as numerical values and

using the categories defined in the literature[11] among patients who developed ulcers at different stages and those who did not. However, we found no statistically significant results, leading us to conclude that the Braden risk assessment system is ineffective in predicting pressure ulcers caused by oronasal masks used for NIMV.

Key Findings

One of the most critical findings of our study was that while the daily duration of mask use did not significantly influence the development of pressure ulcers, the number of days masks were used was a significant factor. Starting from the sixth day, patients with stage 1 pressure ulcers showed a significantly higher risk of progression to stage 2 ulcers as the number of days of mask use increased. This trend continued on the ninth day. Similarly, a study by Ferrari et al.[14] which analyzed risk factors for device-related pressure ulcers in patients using NIMV, found that the use of oronasal masks, the duration of ventilation, the type of nutritional support, and chronic corticosteroid use were associated with ulcer development. However, in our study, no relationship was found between the number of corticosteroid use days, daily dosage, or total dosage and pressure ulcer development. We did, however, identify the number of days masks were used as a risk factor for ulcer progression from redness (stage 0>>stage 1) to ulcer formation (stage 1>>stage 2). Visscher et al.[15] emphasized the importance of proper mask selection and moisturizing the skin to prevent such developments.

Nutritional status, albumin levels, and BMI values in our patients were not associated with device-related pressure ulcer development. In the literature, both high and low BMI values have been identified as risk factors for pressure ulcer development.[16,17] Additionally, low albumin levels and malnutrition are recognized as risk factors.[16] A study by Chen et al.[18] described a "U-shaped" relationship between BMI and pressure ulcer risk, indicating that both high and low BMI values pose a risk.

Another significant finding was the length of ICU stay. Patients who stayed longer in the ICU were significantly more likely to have their ulcers progress to stage 3. This raises a potential paradox: do longer ICU stays increase the risk of pressure ulcers, or do pressure ulcers prolong ICU stays? Many studies have emphasized that pressure ulcers significantly extend ICU stays.[19,20] However, our study specifically focused on oronasal masks, and our patients already had ICU stays prior to mask use. It is possible that patients with longer ICU stays had more comorbidities, which worsened their ulcers.

Lastly, we observed that patients with stage 1 ulcers had significantly lower BUN levels compared to those without ulcers. A study conducted in a surgical ICU reported significantly higher BUN/creatinine ratios in patients with pressure ulcers.[21] Another study suggested two perspectives on high BUN levels: they may either indicate reduced vasodilatory mediators from the kidney, delaying wound healing and increasing ulcer risk, or they may reflect good nutritional status.[22] In our study, we associated high BUN levels with good nutrition. Moreover, the median and minimum-maximum BUN values of our patients indicate that none had BUN levels suggestive of acute or chronic renal dysfunction. Although we found that higher BUN levels were associated with fewer device-related pressure ulcers in our study, future research with a larger patient cohort and higher BUN levels is necessary to determine whether similar results can be reproduced. To achieve more robust and realistic findings, patients could be stratified into quartiles based on BUN levels, allowing for a comparative analysis of four distinct patient groups. Statistical analyses conducted using this approach may reveal a U-shaped relationship, where both extremely high and extremely low BUN levels are associated with an increased risk of pressure ulcers, thereby potentially supporting both our findings and the existing literature.

Limitations

The limitations of our study include the relatively small sample size, primarily due to the exclusion of patients discharged before the required follow-up period. Additionally, the retrospective design, single-center setting, and focus on a single type of medical device limit the generalizability of our findings.

CONCLUSION

We believe that the three valuable and significant findings of our study should be considered during the follow-up processes of patients undergoing NIMV with an oronasal mask due to respiratory failure. Based on the data indicating that pressure ulcers improved in patients with moderately elevated BUN levels, reflecting a positive nitrogen balance, we recommend a protein-rich diet to both prevent the development of pressure ulcers and improve respiratory functions. Furthermore, to reduce device-related pressure ulcers, we emphasize the importance of minimizing the number of days patients use the mask and avoiding unnecessary prolongation of hospital stays during NIMV treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval was obtained from the Clinical Researches Ethics Committee of the University of Health Sciences, Ankara Keçiören Training and Research Hospital (Date: 25.01.2022, Decision No: 2012-KAEK-15/2467).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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Review

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Substance use and memory impairments: a multidimensional review on neurological and cognitive effects

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ABSTRACT

This study aimed to examine the relationship between substance use and memory disorders. This study also analyzed the biological effects of drug use on the brain and investigated the mechanisms by which these effects lead to impairment of memory function. Furthermore, the impact of various elements, including substance abuse, mental health conditions, hereditary susceptibility, and chronological age, was assessed. Substance use negatively affects memory and learning processes by causing functional impairments in critical regions such as the hippocampus and frontal lobe. Different substances cause specific damage to the memory. This review highlights how substance use can lead to permanent neurocognitive impairment, with effects varying according to substance type, duration of use, and individual factors. This underscores the importance of early intervention and preventive strategies. Multidisciplinary approaches are important in the prevention and management of these effects.

Keywords: Substance addiction, memory disorders, cognitive effects

INTRODUCTION

Substance use and addiction are considered important public health problems that create complex effects not only at the individual level but also on a social and global scale. Recent studies have emphasized the escalating global burden of substance use disorders, necessitating updated reviews. To understand this phenomenon and to develop effective intervention methods, there is a need to comprehensively address the prevalence, causes, and consequences of substance abuse. This study aims to fill a gap in the literature by synthesizing evidence on how substance use impairs memory, a critical yet underexplored cognitive outcome, compared to broader addiction research. Researchers have developed various theoretical approaches to explain the effects of substance use on individuals and the mechanisms underlying these effects and have presented experimental findings that support these approaches.

According to the 2023 World Drug Report published by the United Nations Office on Drugs and Crime, approximately 296 million people aged 15-64 used drugs at least once in 2022, an increase from 275 million in 2021, reflecting a growing challenge.[1] This rate is significantly higher among men than women. In Turkey, 6.1% of men and only 0.3% of women use drugs at some point in their lives.[2] When the relationship between substance use and socioeconomic conditions is analyzed, factors such as low-income level, unemployment, and low education level increase the prevalence of this problem. Social factors such as gender roles and cultural norms also shape substance use tendencies. The causes and dynamics of substance use can be explained using various theoretical frameworks. These frameworks consider substance use a complex interaction of biological, psychological, and social factors, encompassing a wide range of influences that lead individuals to such behaviors.

The biopsychosocial model is a multifaceted approach that explains substance use through the interaction of biological, psychological, and social factors. Genetic predisposition, neurobiological processes, personality traits, family structure, environmental stress factors, and cultural norms were the main components of this model. Research has emphasized the role of genetic factors in the development of addiction. Kreek et al.[3] suggested that genetic components of addiction predisposition can explain approximately 30% of addictive behaviors, which was updated by Wright et al.[4] The genetic basis of substance use remains a key focus of addiction research. The effects on the dopamine system are among the neurobiological mechanisms underlying addiction. The allostasis theory, developed by Koob and Le Moal,[5] argues that addiction leads to continuous adaptation in the brain's reward system, making it a chronic condition.[5,6] This theory explains the long-term negative effects of substance addiction on brain neuroplasticity. Psychological coping skills related to stress and emotional regulation strategies are also critical factors that affect susceptibility to addiction.

The examination of substance use within the framework of the social learning theory reveals the importance of

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environmental influences and observational learning. Bandura's[7] theory posits that individuals can learn substance use by observing and modeling behaviors around them. Peer influence and role models encourage substance use, especially among the youth. Positive reinforcement mechanisms motivate their continued use. Agnew's[8] tension theory suggests that efforts to cope with stress and social pressure may trigger substance use. Socioeconomic problems, family conflicts, and unemployment often drive individuals toward alcohol or drugs.[9] Studies show that those experiencing economic difficulties are more likely to turn to substances. Subculture theory argues that certain social groups normalize substance use, reinforcing a sense of belonging, particularly in youth subcultures. Cohen's[9] subculture theory suggests these groups strengthen individuals' willingness to challenge social norms. Psychodynamic theory links substances to early life experiences and unresolved internal conflicts. Khantzian[10] defined addiction as an attempt to alleviate psychological pain, noting higher risks in individuals with childhood trauma. These theoretical approaches to substance use explain different aspects of the phenomenon and contribute to a multidimensional understanding. However, each of these theories focuses on only one specific aspect of substance use, and does not fully reflect the complexity of the situation. These frameworks collectively suggest a multifaceted etiology, necessitating holistic interventions.

Substance abuse and addiction are complex problems that reduce the quality of life of individuals, consume social resources, and threaten public health globally. Among the negative effects of this problem, memory impairment, which also affects cognitive skills, is particularly important. These impairments in memory processes indicate that substance use can negatively affect individuals' daily lives and functionality. In this context, the causes of theoretical approaches to memory disorders help us better understand this complex problem.

MEMORY DISORDERS

Memory disorders are among the most complex and multidimensional cognitive problems. Theories explaining these disorders have shed light on various aspects of memory processes, offering perspectives from cognitive psychology, neuroscience, and neuropsychology. The neuroplasticity theory of memory disorders focuses on the brain's capacity to change and adapt.[11] This theory suggests that memory disorders arise from the weakening or loss of synaptic connections, a mechanism critical in neurodegenerative diseases such as Alzheimer's and substance abuse.[11] In Alzheimer's patients, the loss of neurons in the hippocampus and other limbic system structures and the decrease in synaptic connections cause individuals to experience serious difficulties in the process of forming and storing new memories.[12] Studies show that beta-amyloid plaque accumulation disrupts synaptic plasticity, directly affecting short-term memory. This theory also applies to memory deficits caused by traumatic brain injury, epilepsy, and substance abuse. The processing speed theory explains memory impairments related to aging and substance use.[13] A decrease in information-processing speed with age negatively affects working memory performance, causing difficulties in encoding and recalling new information. Research indicates that older individuals process information more slowly than younger ones, impacting memory, especially during multitasking.[13] For example, an elderly individual's difficulty in remembering a recently learned phone number is due to their inability to process information quickly enough, and chronic alcohol users show a 20% reduction in processing speed, leading to significant declines in short-term and working.[14] The decrease in white matter density with age or substance-induced damage slows neural transmission further. According to this theory, substance use, especially long-term consumption of substances that damage the central nervous system, leads to a significant decrease in the speed of cognitive processes and this slowdown in processing speed directly affects memory processes and creates difficulties in encoding, storing and recalling new information.[15,16] Substances like alcohol, cocaine, and cannabinoids damage nerve cells or disrupt neurotransmitter balances, exacerbating this slowdown.[17] Longitudinal studies of methamphetamine users confirm reduced processing speed impacts episodic memory.[17] These findings emphasize that the processing speed theory provides a powerful model to explain substance use-induced memory impairments and the importance of focusing on processing speed in cognitive rehabilitation processes of substance use.

The Activation-Monitoring Theory explains memory errors and false memories. This posits that recalling information activates related data, sometimes leading to false recall. This is common in eyewitness cases, where details heard later are misremembered as true. For example, a crime witness's recollection of details that he/she did not see at the time of the incident but heard later as a true memory can be explained by this theory.[18] Laboratory studies show that false information can integrate into memory processes, facilitating false memories.[19] Substance use increases source errors by disrupting neurotransmitter activity in the prefrontal cortex and hippocampus.[20] For example, experiments in individuals under the influence of alcohol have shown that false memories frequently increase because of weakened memory monitoring mechanisms.[21] Similarly, a study in individuals using cannabis found that they were more likely to falsely link memory sources under the influence of the substance.[22] These findings suggest that activation-monitoring theory states that specific memory errors, such as false memories, may occur more commonly as a result of substance use. Alcohol weakens memory monitoring mechanisms, increasing false memories, while cannabis use heightens the likelihood of misattributing memory sources.[23]

The Fuzzy Trace Theory posits two memory systems: verbatim traces for detailed recall and gist traces for general meaning. Memory impairments often involve loss of verbatim traces, making detailed recall difficult. This theory explains why some individuals have difficulty remembering specific details while remembering general information.[24] For example, in neurological examinations, it has been observed that patients with dementia can recall the general outline of an event but cannot provide clear information about its details. The loss of specific traces makes it difficult to maintain the clarity and detail of memories. Patients with dementia, for instance,

recall events that are outline, but not specific. Substance abuse, particularly alcohol and drugs, weakens verbatim traces, leading to reliance on gist traces and inaccurate recall.[25] Multiple Trace Theory suggests episodic memories are reconstructed over time through multiple neural traces between the hippocampus and cortical areas. Substance abuse disrupts these traces, weakening episodic memory and making it less detailed over time.[26]

Theories explaining memory disorders provide an in-depth understanding of the factors that influence cognitive functioning, showing how both neurological and environmental influences are reflected in memory processes.[27,28] Each theory emphasizes different aspects of memory mechanisms, and details the effects of substance use on impairments in these mechanisms. In this context, substance use appears to have multifaceted effects, ranging from synaptic plasticity to the reconstruction of episodic memories, from decreased processing speed to the formation of false memories.[29] The explanations offered by these theories provide an important basis for understanding the multidimensional effects of substance use on memory.[30] In which the complex effects of substance use on memory will be elaborated, and reflections of this situation on cognitive functions will be discussed.

METHODS

This review systematically analyzes the current scientific literature on the relationship between substance use and memory impairments. Studies were selected based on predefined inclusion and exclusion criteria, and relevant data sources were systematically searched using specific keywords. The data for this study were obtained from major scientific databases including PubMed, PsycINFO, Scopus, and Web of Science. Peer-reviewed articles published between 2010 and 2024 were prioritized, with a focus on both empirical research and meta-analysis. Case reports, letters to the editor, and print articles were excluded. Studies were selected based on specific inclusion criteria such as examining the relationship between substance use and memory processes, assessing memory functions through neuropsychological measures, and including human participants in experimental or observational designs. Exclusion criteria included studies that relied solely on animal models, had small sample sizes or significant methodological limitations, and did not specifically assess memory-related outcomes in substance users.

A comprehensive literature search was conducted using Boolean operators (AND, OR) to combine relevant keywords, including "substance use" AND "memory impairment," "drug abuse" AND "cognitive decline," "alcohol use" AND "working memory," "neurotoxicity" AND "memory function," and "cannabis" AND "episodic memory." The search results were filtered, and only studies that met the eligibility criteria were included in the analysis.

The selected studies were analyzed using a content analysis approach to compare the findings across different research methodologies. The findings were categorized into key themes such as the neurobiological mechanisms underlying substance-induced memory impairments, variations in memory deficits based on substance type, and the impact of age on cognitive decline related to substance use. This methodological framework ensures a systematic and comprehensive approach for understanding the multifaceted effects of substance use on memory processes. This analysis provides insights into how different substances affect memory functions and highlights the importance of early intervention strategies.

MULTIDIMENSIONAL EFFECTS OF SUBSTANCE USE ON MEMORY

The relationship between substance use and memory disorders is complex and multifaceted. This relationship stems from various factors, such as the direct effects of substance use on the brain, chronic use leading to neurological changes, and the effects of substance use disorder on the lifestyle of individuals.[31] The mechanisms underlying this relationship have been discussed in detail in the literature, and a better understanding of these mechanisms is important for developing strategies to solve this problem. Recent studies have revealed important findings on this issue by examining the different dimensions of substance use more comprehensively.

Substance use exerts multifaceted effects on memory through direct neurotoxic effects and indirect lifestyle changes. Chronic alcohol consumption, for example, has been associated with a reduction of hippocampal volume by up to 15%, leading to significant episodic memory deficits and even neurological conditions such as Wernicke-Korsakoff syndrome.[32,33] Cannabinoids have also been reported to weaken learning processes by affecting glutamate release in the brain.[34] The effects of substance use on neurotransmitter systems further complicate memory processing and storage processes.[35] Volkow and Fowler[30] revealed that imbalances in dopamine systems directly negatively affect cognitive performance, especially by affecting motivation and reward perception. Chronic substance use causes long-term changes in structural and functional properties of the brain. Long-term methamphetamine use has been shown to cause neuronal death and decrease synaptic connections in regions such as the frontal lobe, caudate nucleus, and hippocampus.[36] Such damage may permanently affect cognitive functions, such as self-control, decision-making, and memory. Pfefferbaum and Sullivan[37] demonstrated that chronic alcohol use causes severe disruptions in white matter structure and a marked decrease in neurocognitive performance. Similarly, neurological diseases such as Wernicke-Korsakoff syndrome occur due to alcohol use and increase the severity of memory impairments. In addition, cocaine use has been reported to cause irreversible damage to the dopaminergic system of the brain, leading to long-term problems in memory processes.[38]

The effects of substance use disorder on lifestyle indirectly negatively affected memory function. For example, substance use leads to disruptions in sleep patterns and malnutrition.[39] Lack of sleep negatively affects synaptic reorganization, which is a critical process in memory consolidation, making it difficult to learn and store new information.[40] In addition, studies on malnutrition have shown that vitamin B deficiency negatively affects neuronal health and memory function.[41] For example, Falletti et al.[42] reported that vitamin deficiencies that

occur during substance abuse lead to more serious memory problems, especially in individuals who consume alcohol.

The effects of substance use depend on the type of substance being used. While alcohol has more pronounced negative effects on episodic memory, amphetamine and cocaine, which are stimulant substances, affect working memory and attention processes.[43] Substances with strong neurotoxic effects, such as methamphetamine, cause more rapid and permanent brain damage than other substances.[44] In addition, the depressant effects of opioids affect an individual's memory performance in a more complex manner by impairing decision-making and emotional processing. Ersche et al.[45] reported that long-term cocaine use leads to a significant decrease in working memory capacity. In this study, the effects of long-term cocaine use on cognitive function were addressed, especially changes in working memory capacity. This study was based on comparisons between long-term cocaine users and healthy controls. Participants were administered various neuropsychological tests, and their working memory capacity, attentional control, and executive function were assessed. The results revealed that cocaine users experienced a marked reduction in working memory capacity compared with the control group. This reduction was associated with difficulties in holding and manipulating information over short periods. The researchers explained this by the fact that cocaine disrupts the neurotransmitter balance in the prefrontal cortex and negatively affects neural plasticity. Furthermore, these cognitive impairments were observed to increase with duration and intensity of use.

AGE EFFECT ON SUBSTANCE USE AND MEMORY DISORDERS

The age at which substance use begins plays a crucial role in determining the severity and longevity of memory and cognitive impairments. The adolescent brain, which is still in a critical phase of development, is particularly vulnerable to the neurotoxic effects of substance use. During this period, the brain undergoes significant structural and functional changes, with key processes such as synaptic pruning, myelination, and strengthening of neural circuits. These developmental changes make the brain more susceptible to the damaging effects of drugs and alcohol, potentially leading to long-term deficits in cognitive function, including memory, attention, and executive function.

Research has consistently shown that early substance use during adolescence can cause irreversible damage to the brain regions responsible for memory processing, such as the hippocampus and prefrontal cortex. For instance, studies have demonstrated that adolescent alcohol use leads to a reduction in hippocampal volume, which is linked to difficulties in episodic memory and learning.[32] Furthermore, substance use during adolescence disrupts the development of the prefrontal cortex, a brain region involved in working memory, decision making, and impulse control, thereby impairing cognitive abilities that are critical for academic and social functioning.

One of the key factors contributing to adolescents' vulnerability to substance-induced memory deficits is the high degree of neuroplasticity during this stage of life. While neuroplasticity allows for learning and adaptation, it also means that the brain is easily altered by external factors, including substance use. The neurotoxic effects of substances such as alcohol, marijuana, and stimulants can interfere with the normal brain maturation process, potentially leading to enduring cognitive deficits. For example, chronic cannabis use during adolescence has been associated with long-term impairments in working memory and executive function.[19]

The long-term impact of adolescent substance use on memory is compounded by the fact that many individuals who begin using substances at an early age are at a higher risk of developing substance use disorders later in life. The combination of early exposure to substances and development of substance use disorders significantly increases the likelihood of developing cognitive deficits in adulthood. Studies have shown that individuals who began using alcohol or other drugs in their teenage years exhibit more pronounced cognitive decline in adulthood compared to those who initiated use later in life.[46,47]

In addition to the direct neurotoxic effects of substances on the developing brain, lifestyle changes associated with early substance use, such as poor nutrition, disrupted sleep patterns, and increased risk of mental health issues further exacerbate memory problems. The impact of poor nutrition, for example, is particularly concerning during adolescence, which is marked by rapid physical and cognitive growth. Deficiencies in essential nutrients, such as vitamin B and omega-3 fatty acids, can impair neuronal function and exacerbate memory deficits in adolescents who use substances regularly.[42]

Recent studies have also highlighted the role of genetic factors in shaping adolescents' vulnerability to substance-induced memory impairments. Genetic variations in genes involved in neurotransmitter systems, such as COMT and BDNF, may predispose some individuals to severe cognitive deficits following substance use. Adolescents with these genetic predispositions may experience a greater degree of neurotoxic damage to brain structures involved in memory, making them more susceptible to long-term cognitive impairments.[4]

Moreover, the effects of early substance use were not limited to memory deficits. Adolescents who engage in substance use are also at risk of developing other cognitive and emotional challenges, including difficulties with attention, problem-solving, and emotional regulation. When combined with the social and academic pressures that adolescents face, these cognitive impairments can have a lasting impact on their overall well-being and development. As these individuals transition into adulthood, the consequences of early substance use can persist, potentially affecting their ability to succeed in the workforce and to maintain healthy relationships.

GENETIC FACTORS ON SUBSTANCE USE AND MEMORY DISORDERS

Genetic factors play a crucial role in mediating the relationship between substance abuse and memory disorders. While environmental influences, such as early exposure to substances and lifestyle factors, undoubtedly contribute to cognitive impairment, genetic predisposition can significantly amplify or modulate the effects of substance use on brain

function, particularly memory. Research into the genetic underpinnings of substance use disorders (SUDs) and their neurocognitive consequences has revealed important insights into why certain individuals are more susceptible to substance-induced memory deficits than others. One of the key areas of focus in genetic studies of substance use and memory is the role of neurotransmitter systems, particularly those involving dopamine, glutamate, and serotonin. Variations in the genes that regulate these systems can influence how the brain responds to substances and, subsequently, how memory processes are affected. For instance, the gene encoding the catechol-COMT enzyme, which regulates dopamine metabolism in the prefrontal cortex, has been linked to individual differences in cognitive function. Studies have shown that individuals with certain COMT polymorphisms, specifically the Val158Met variant, may experience more severe cognitive impairments, including memory dysfunction, when exposed to substances such as alcohol or amphetamines.[4] This genetic variation may make the brain more vulnerable to neurotoxic damage, thereby increasing the risk of developing long-term memory deficits following substance abuse. Another gene of significant interest is brain-derived neurotrophic factor (BDNF), which plays a critical role in synaptic plasticity, learning, and memory. BDNF facilitates the growth, maintenance, and survival of neurons, and its expression is strongly influenced by environmental factors, including substance use. Genetic variants of the BDNF gene, particularly the Val66Met polymorphism, have been shown to impair hippocampal-dependent memory functions such as spatial memory and long-term memory consolidation. These genetic differences can make individuals with certain BDNF variants more susceptible to cognitive impairments associated with chronic substance use.[48] Furthermore, BDNF's role of BDNF in neuroplasticity means that individuals with impaired BDNF function may have a reduced ability to recover from the neurotoxic effects of substances, leading to persistent memory deficits even after abstinence. In addition to the genes involved in neurotransmitter regulation, recent research has also identified the role of genes related to neuroinflammation in substance-induced memory dysfunction. Substances such as alcohol, methamphetamine, and cocaine increase neuroinflammation in the brain, which can contribute to neuronal damage, particularly in regions such as the hippocampus that are essential for memory formation and consolidation. Variations in the genes that control the brain's immune response, such as those in the interleukin (IL) and tumor necrosis factor (TNF) families, can influence the degree of neuroinflammation that occurs in response to substance use. Individuals with certain genetic predispositions to higher levels of neuroinflammation may experience more severe damage to brain structures involved in memory, leading to more pronounced cognitive deficits.[11] The genetic susceptibility to memory disorders associated with substance use is not only a matter of individual genetic differences but also the interaction between genetic factors and the timing of substance use. For instance, individuals with a genetic predisposition to addiction and cognitive impairment may be especially vulnerable to the neurotoxic effects of substances when exposure occurs during critical periods of brain development, such as adolescence. During this stage, the brain still undergoes significant maturation, and the impact of substances such as alcohol or marijuana may be particularly damaging. In such cases, genetic vulnerabilities can be exacerbated by the early initiation of substance use, leading to long-term and often irreversible cognitive deficits, including memory impairments.[47]

The role of epigenetics in substance-induced memory dysfunction is gaining increasing attention. Epigenetic modifications, which involve changes in gene expression without altering the underlying DNA sequence, can be influenced by environmental factors such as substance use. These modifications can have lasting effects on brain functions, including memory. For example, research has shown that chronic substance use can lead to changes in DNA methylation patterns in brain regions involved in memory processes, such as the hippocampus. These epigenetic changes may not only affect the individual who is using substances but could also be passed down to future generations, potentially increasing the risk of memory impairments in offspring.[49]

The interaction between genetic factors and psychiatric conditions further complicates the relationship between substance use and memory disorders.[50,51] Psychiatric disorders, such as depression, anxiety, and schizophrenia, are often comorbid with substance use disorders, and genetic predispositions to these conditions may enhance vulnerability to cognitive impairments. For example, genetic risk factors for depression, such as polymorphisms in the serotonin transporter (5-HTT) gene, have been linked to increased susceptibility to cognitive deficits caused by substance use, particularly memory and attention.[52] Individuals with both genetic vulnerabilities to psychiatric disorders and a history of substance use may face compounded risks of memory dysfunction, highlighting the need for integrated treatment approaches.

THE RELATIONSHIP BETWEEN PSYCHIATRIC DISORDERS, SUBSTANCE USE, AND MEMORY

The intricate relationship between psychiatric disorders, substance use, and memory dysfunction underscores the complex interplay between genetic, neurobiological, and environmental factors that significantly impact cognitive functioning. Psychiatric disorders, such as depression, anxiety, posttraumatic stress disorder (PTSD), and schizophrenia, commonly co-occur with substance use disorders (SUDs), which complicate the cognitive and emotional processes associated with substance use, particularly memory. Research has demonstrated that substance use not only exacerbates psychiatric symptoms, but also negatively affects cognitive domains, including memory, attention, and executive functioning.

Memory deficits are frequently observed in individuals with psychiatric disorders even in the absence of substance use. For example, depression has been consistently linked to cognitive impairment, particularly in the areas of working and episodic memory. These deficits are thought to arise from neurobiological changes in brain regions, such as the

prefrontal cortex and hippocampus, which are essential for memory processing. A meta-analysis by McDermott et al.[53] revealed that individuals with major depressive disorder (MDD) exhibit significant impairments in verbal and non-verbal memory tasks. These impairments are believed to be mediated by the disruption of hippocampal neurogenesis and alterations in the serotonin and dopamine systems, which play critical roles in memory formation and consolidation. Furthermore, depressive symptoms, including low motivation and anhedonia, may indirectly impair memory by reducing engagement in cognitive activities and social interactions that are essential for cognitive preservation. Anxiety disorders also contribute to memory dysfunction, particularly by impairing the working memory and attentional control. Chronic stress, a hallmark of anxiety disorders, can increase levels of cortisol, a hormone that negatively affects hippocampal function. Elevated cortisol levels can disrupt the encoding and retrieval of memories, particularly in tasks that require attention and integration of new information. For instance, Zhang et al.[54] showed that individuals with generalized anxiety disorder (GAD) had lower scores on working memory tasks than healthy controls, with the degree of impairment being directly related to the severity of anxiety symptoms. This suggests that the persistent physiological and psychological stress associated with anxiety disorders may hinder the brain's ability to process and store new information.

Substance use, whether alcohol, illicit drugs, or prescription medications, has well-documented neurotoxic effects on memory, particularly episodic memory, working memory, and attention. As previously discussed, substances such as alcohol, methamphetamine, cocaine, and opioids can directly impair brain structures involved in memory processing, such as the hippocampus, prefrontal cortex, and the dopaminergic and glutamatergic systems. For example, chronic alcohol use is a major contributor to memory deficits, particularly alcohol-induced cognitive impairment (AICI) and Wernicke-Korsakoff syndrome (WKS). Alcohol-related brain damage leads to a significant reduction in hippocampal volume and disrupts synaptic plasticity, impairing both short-term and long-term memory processes.[32] The neurotoxic effects of alcohol are compounded by nutritional deficiencies, such as thiamine deficiency, which is common in individuals with alcohol use disorder (AUD) and further exacerbates memory dysfunction. Studies have shown that individuals with WKS, a severe form of alcohol-related cognitive impairment, experience profound deficits in episodic memory such as an inability to form new memories or recall recent events. Similarly, stimulant substances, such as methamphetamine and cocaine, can cause severe damage to the dopaminergic and glutamatergic systems, resulting in working memory deficits and impairments in executive function. For example, long-term methamphetamine use has been shown to cause neuronal death in the frontal cortex and hippocampus, which are areas critical for attention, working memory, and decision-making.[30] Cocaine use also leads to substantial alterations in dopamine transmission, which impairs memory consolidation and retrieval. Research by Ersche et al.[45] revealed that long-term cocaine use resulted in significant reductions in working memory capacity, with users exhibiting difficulties in holding and manipulating information for short periods. These impairments are thought to be the result of disrupted neural circuits in the prefrontal cortex and other brain regions involved in memory processing.

The presence of psychiatric disorders in individuals with substance use disorders exacerbates memory dysfunction, leading to a cycle of cognitive decline. Many individuals with SUDs experience psychiatric comorbidities, including depression, anxiety, and PTSD, which further compromise their cognitive performance. This comorbidity is particularly concerning because psychiatric disorders often lead to changes in brain structure and function that overlap with the effects of substance use, amplifying the severity of cognitive impairments. For example, depression and alcohol use disorder often co-occur, with each condition exacerbating the other's symptoms. Depression is associated with reduced hippocampal volume and altered neurotransmitter systems, while alcohol use disorders lead to shrinkage of the hippocampus and disruptions in cognitive function. This combined effect of depression and alcohol use leads to more severe memory deficits than in individuals with alcohol use disorder alone.[52] The cognitive impairments in these individuals are not limited to episodic memory but extend to other domains, including attention and executive function, which are crucial for day-to-day functioning. Anxiety disorders when combined with substance use have similar detrimental effects on memory. Chronic stress and elevated cortisol levels seen in anxiety disorders can exacerbate the neurotoxic effects of substances such as alcohol or cocaine, leading to increased damage to the brain regions responsible for memory. Furthermore, the emotional dysregulation seen in individuals with both anxiety and substance use disorders can impair cognitive flexibility and memory retrieval, making it more difficult for individuals to process and retain information.[55] PTSD is another psychiatric condition that significantly affects memory, particularly intrusive memories and impaired memory consolidation. PTSD often co-occurs with substance use disorders, especially alcohol and cannabis use, because individuals may use substances as a form of self-medication. However, substance use only exacerbates the cognitive dysfunction observed in PTSD. Chronic alcohol consumption in individuals with PTSD can worsen memory problems, particularly those related to emotion regulation and memory retrieval. The dual burden of PTSD and substance use results in heightened vulnerability to severe memory impairments, which can affect both short-term and long-term memory processes.[56]

CONCLUSION

This study examines the multidimensional effects of substance use on memory within the framework of theoretical and empirical evidence. Substance use has been identified as a complex public health issue that adversely affects cognitive function. Specifically, its effects on memory processes have been explored through various mechanisms including synaptic plasticity, information processing speed, memory trace formation, and the emergence of false memories. While existing theoretical frameworks contribute to the understanding of the negative impact of substance use on

memory, no single theory is sufficient to fully explain the complexity of this phenomenon. Therefore, it is necessary to develop holistic models that account for the interplay between biological, psychological, and environmental factors in substance use-related memory impairments.

This study had several limitations. First, the effects of substance use on memory may vary among individuals and are influenced by factors such as genetic predisposition, environmental conditions, and type of substance used. Moreover, the scarcity of longitudinal studies in the literature makes it difficult to comprehensively understand the long-term effects of substance use. The impact of substance use initiated during adolescence on cognitive development requires further investigation. Additionally, the roles of neuroplasticity and epigenetic changes in substance use-related memory impairment remain incompletely understood.

Future research should focus on several key topics. First, further experimental studies are needed to compare the specific effects of different types of substances on memory. Second, longitudinal research should be conducted to examine the progression and potential reversibility of the cognitive impairments associated with substance use. Third, genetic and neuroimaging studies should be emphasized to enhance our understanding of how individual genetic predispositions influence substance use-related memory disorders. Finally, more research is needed on the effectiveness of intervention and rehabilitation programs and how these programs contribute to the improvement of memory functions in individuals with substance use disorders.

The findings of this study have significant implications for the development of prevention and intervention strategies for substance use. It is essential to consider not only the physical aspects of substance dependence but also the cognitive and psychosocial consequences of treatment approaches. Cognitive rehabilitation techniques and psychosocial support programs designed to enhance memory function can play a crucial role in improving cognitive performance in individuals with substance disorders. In conclusion, a comprehensive and interdisciplinary approach should be adopted to mitigate the adverse effects of substance use on memory, and strategies should be developed to preserve the cognitive function of affected individuals.

ETHICAL DECLARATIONS

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The authors have no conflicts of interest to declare.

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

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Review

MEDICINE PALLIATIVE CARE

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Dyspnea management in palliative care: current approaches and treatment strategies

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ABSTRACT

Dyspnea is a common and challenging symptom to manage in palliative care patients. This review discusses the pathophysiology, assessment methods, and current treatment approaches for dyspnea based on the existing literature. Both pharmacological (opioids, benzodiazepines, glucocorticoids) and non-pharmacological (oxygen therapy, respiratory therapy, environmental modifications) treatment strategies are examined in detail, with a discussion on their efficacy and potential side effects. This study is a narrative review compiling the current literature on the topic.

Keywords: Dyspnea, palliative care, symptom management, multidisciplinary approach

INTRODUCTION

Dyspnea is a complex respiratory symptom with distinct sensory components that is individually perceived.[1] Commonly encountered in palliative care patients, this condition arises from interactions among the respiratory, cardiovascular, and neurological systems. Dyspnea is not merely a physical symptom but a complex condition involving psychological and emotional dimensions. Effective management of dyspnea, which significantly impacts patients' quality of life, is a fundamental goal in palliative care practices. The diagnosis and management of dyspnea vary according to the patient's clinical condition and the progression of the disease. Moreover, dyspnea is a significant source of stress for both patients and their caregivers, making it a complex symptom that requires a multidisciplinary approach.

PREVALENCE OF DYSPNEA

Dyspnea is one of the most common symptoms negatively affecting the quality of life in patients with advanced-stage diseases. Studies indicate that dyspnea is prevalent among patients with terminal-stage cancer, chronic obstructive pulmonary disease (COPD), heart disease, AIDS, or kidney disease.[2-5] The frequency and severity of the symptom increase during the final months of life, causing significant discomfort for patients.[6,7] In the course of chronic diseases, the management of dyspnea requires consideration of both its physiological and psychosocial components.

PATHOPHYSIOLOGY

Dyspnea is a multidisciplinary symptom that arises from the complex interactions between the central nervous system, the respiratory and cardiovascular systems, and psychological factors.[1] The neurophysiological control of respiration is regulated through the respiratory centers in the medulla oblongata, which receive inputs from peripheral chemoreceptors (carotid bodies and aortic bodies), central chemoreceptors, and mechanoreceptors.[8] Dyspnea can develop as a result of dysfunctions in one or more of these mechanisms.

The perception of dyspnea can be described by patients in various ways, such as "air hunger," "increased breathing effort," or "chest tightness." These different perceptions reflect the diversity of underlying pathophysiological mechanisms. These mechanisms include:

Mechanical Load and Muscle Fatigue

The respiratory muscles, including the diaphragm, intercostal muscles, and accessory respiratory muscles, perform the essential mechanical function of maintaining ventilation. However, excessive loading or functional insufficiency of these muscles can impair adequate ventilation, leading to dyspnea. For instance, in pulmonary fibrosis, despite increased effort by the respiratory muscles due to reduced lung compliance, sufficient tidal volume cannot be achieved, contributing to dyspnea development.

Gas Exchange Impairments

Gas exchange in the lungs is maintained through the balance between alveolar ventilation, diffusion capacity, and perfusion. Conditions such as hypoxia or hypercapnia enhance respiratory drive, triggering the sensation of dyspnea.[9] For example, in pulmonary embolism, ventilation

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remains intact, but perfusion is disrupted, leading to hypoxia and the subsequent onset of dyspnea.

Cardiogenic Factors

Dyspnea is not solely limited to respiratory pathologies but is also associated with cardiovascular diseases such as heart failure.[10] Cardiac-origin dyspnea typically arises due to increased pulmonary capillary pressure secondary to pulmonary congestion. Elevated pulmonary venous pressure leads to interstitial edema and alveolar fluid accumulation, impairing gas exchange. Even in the absence of hypoxia, these mechanisms can trigger the sensation of dyspnea.

Airway Resistance and Flow Limitation

Increased airway resistance contributes to greater respiratory effort during both inspiration and expiration, resulting in dyspnea. In conditions such as asthma and COPD, airway inflammation and narrowing restrict airflow, particularly during expiration, thereby increasing respiratory workload and promoting dyspnea.

Psychological and Neurological Mechanisms

Dyspnea is a complex sensory experience processed within the central nervous system. The cortical perception of breathlessness arises from the integration of respiratory center signals from the brainstem with processing in brain regions such as the insula, anterior cingulate cortex, prefrontal cortex, and amygdala.[11] This process is influenced not only by respiratory and cardiovascular inputs but also by emotional and cognitive factors. Notably, the amygdala, which is associated with anxiety and fear responses, can heighten the perception of dyspnea, leading patients to experience respiratory distress more intensely.[12] Consequently, effective dyspnea management should not only involve mechanical and pharmacological interventions but also incorporate strategies targeting cognitive and psychological factors.

The causes of dyspnea and its pathophysiological mechanisms are presented in Table 1.

Table 1. Pathophysiological classification of diseases causing dyspnea

Category	Diseases/conditions	Primary mechanism
Obstructive	COPD, asthma, bronchiectasis, central airway obstruction	Airflow limitation, airway inflammation
Restrictive	Pulmonary fibrosis, thoracic deformities, neuromuscular diseases	Decreased lung compliance, respiratory muscle weakness
Cardiogenic	Heart failure, pulmonary hypertension, myocardial infarction	Pulmonary congestion, reduced cardiac output
Psychogenic	Anxiety, panic disorder	Hyperactivity of the respiratory control center
Mechanical	Diaphragmatic paralysis, chest wall deformities	Respiratory muscle dysfunction
Hematologic	Anemia, carbon monoxide poisoning	Decreased oxygen-carrying capacity
Vascular	Pulmonary embolism, pulmonary hypertension	Perfusion impairment, right ventricular failure

ASSESSMENT

The assessment of dyspnea aims to determine the severity of the symptom, the progression of the underlying disease, and its impact on the patient's quality of life. Patients may describe dyspnea in various ways, making it essential to consider their individual experiences during the clinical evaluation. Common assessment methods include numerical rating scales, visual analog scales, and functional assessment tools. The Memorial Symptom Assessment Scale and the Edmonton Symptom Assessment Scale are frequently used in clinical practice.[13,14] Evaluating changes in patients' functional capacities and daily activities provides valuable insights into dyspnea management. Key aspects of the clinical evaluation include how patients describe their dyspnea, the timing of its onset, and the conditions under which it occurs.

PSYCHOLOGICAL IMPACTS OF DYSPNEA

Dyspnea is not merely a physical symptom but also exerts significant psychological and social effects on patients.[15] It is commonly associated with anxiety, depression, and social isolation, which can subsequently lower the patient's quality of life. Particularly in advanced-stage patients, the sensation of breathlessness is often linked to a sense of proximity to death, leading to heightened anxiety and panic attacks.[16] Anxiety can exacerbate the severity of dyspnea by increasing respiratory effort. Therefore, psychosocial support and anxiety management should be integrated into the treatment process. Psychological support is a crucial component of the patient-centered care approach in palliative care settings.[17] For these reasons, dyspnea management must address not only the physical symptoms but also the psychosocial needs of the patient.

TREATMENT AND MANAGEMENT

The primary goal of dyspnea treatment is to alleviate the patient's discomfort and improve their quality of life. An integrated strategy involving both pharmacological and non-pharmacological approaches is essential. Treatment options should be tailored based on the patient's clinical condition, symptom severity, and underlying diseases.

Targeted Treatments Addressing Underlying Causes of Dyspnea

In dyspnea management, alongside symptomatic approaches, targeted treatments addressing underlying causes can also be implemented.[18] Identifying various etiological factors such as COPD, central airway obstruction, heart failure, lymphangitic carcinomatosis, and malignant pleural effusions allows for the individualization of treatment strategies.

MANAGEMENT

COPD and Dyspnea Management

COPD is one of the most common conditions leading to dyspnea and is frequently observed in advanced cancer patients, particularly those with a history of smoking. In this patient group, the assessment and management of airway obstruction are of critical importance. While bronchodilator

therapy can provide symptomatic relief, pulmonary rehabilitation programs—aimed at improving exercise tolerance and offering psychosocial support—can enhance patients' quality of life. However, for patients with a limited life expectancy, the effectiveness of pulmonary rehabilitation may be restricted.

Idiopathic Pulmonary Fibrosis and Dyspnea Management

Despite having a worse prognosis compared to many malignancies, patients with idiopathic pulmonary fibrosis (IPF) often do not receive adequate palliative care. In a study conducted by Arı et al.[19], the mortality rate of patients treated in intensive care due to an acute exacerbation of IPF was reported to be 62.7%. Similarly, a survey conducted by Akiyama et al.[20] among pulmonologists revealed that providing palliative support to patients with IPF posed greater challenges compared to lung cancer patients. These findings highlight the necessity of developing and prioritizing specialized palliative care programs tailored for patients with IPF.

Lung Malignancies and Dyspnea Management

Lung malignancies can lead to the development of dyspnea, particularly in advanced stages.[18] The primary mechanisms contributing to dyspnea in lung cancer include airway obstruction due to tumor burden, pleural effusion, lymphangitic carcinomatosis, superior vena cava syndrome, and lung injury secondary to radiation or chemotherapy.[21] In the management of dyspnea associated with lung malignancies, both symptomatic approaches and treatments targeting the underlying disease are crucial.

Airway obstruction due to tumor burden: Endobronchial tumors can be debulked using bronchoscopic techniques such as laser therapy, electrocautery, argon plasma coagulation, and cryotherapy.

Pleural effusion: Symptomatic relief can be achieved through therapeutic thoracentesis, placement of a pleural catheter, or pleurodesis.

Lymphangitic carcinomatosis: Glucocorticoids and diuretics may help control symptoms.

Superior Vena Cava Syndrome: Radiotherapy, chemotherapy, or intravascular stent placement can improve venous return and alleviate dyspnea.

In cases of dyspnea caused by central airway obstruction, glucocorticoids can enhance airflow through their tumor-reducing effects.[22] Techniques such as endobronchial laser, electrocautery, argon plasma coagulation and cryotherapy can be used to reduce tumor tissue and provide palliative respiratory support with airway stents. However, careful evaluation is necessary to ensure that such invasive interventions align with the patient's overall care goals.

In patients with end-stage heart failure, dyspnea may develop due to pulmonary congestion, where diuretic therapy can be beneficial. Similarly, in cases of lymphangitic carcinomatosis, diuresis and glucocorticoids have been reported to provide symptomatic relief.[23] Malignant pleural effusions are another significant cause of dyspnea, and treatment options include therapeutic thoracentesis, placement of an indwelling pleural catheter, pleurodesis, and, in rare cases, pleuroperitoneal shunt procedures.

Additionally, glucocorticoids can be used in the management of various causes of dyspnea, including COPD exacerbations, superior vena cava syndrome, radiation pneumonitis, and chemotherapy-induced pneumonitis.[24] In this context, determining individualized treatment approaches targeting the underlying cause of dyspnea is crucial for optimizing symptom control and improving patients' quality of life.

TREATMENTS

Various interventions are utilized in clinical practice to alleviate dyspnea. These include non-pharmacological approaches such as multidimensional dyspnea management programs, graded exercise therapy, increased airflow, breathing techniques, and supplemental oxygen, alongside pharmacological treatments like opioids.[25]

Pharmacological Treatments

Use of opioids in dyspnea management: Opioids play an important role in the management of dyspnea in palliative care.[26] Their use in dyspneic patients reduces respiratory effort, facilitating easier breathing. Opioids act on the central nervous system, decreasing the perception of dyspnea and providing a sense of respiratory comfort. Studies have demonstrated that opioids are effective in alleviating dyspnea during the terminal stages of cancer and chronic diseases.[18]

Opioid dosages and administration methods: Opioids can be administered orally, subcutaneously, or intravenously for the treatment of dyspnea. The dosage and route of administration are determined based on the severity of the patient's symptoms and their tolerance to opioids:

- **Initial dose for patients not using opioids:** Oral morphine 5 mg every 4 hours can be initiated, with additional 2.5 mg rescue doses as needed. Alternatively, for subcutaneous administration, 2.5-3 mg of morphine every 4 hours can be given.
- **Dose adjustment for opioid-tolerant patients:** The dosage may be increased by 25-50% based on the patient's current opioid use.
- **For severe dyspnea crises:** IV morphine can be administered at 2.5-5 mg doses, repeated every 15-30 minutes if necessary.
- **For long-term use:** The total daily dose should be calculated based on the patient's regular daily opioid intake and individualized accordingly.

Side Effects and Precautions of Opioids

The most common side effects of opioids include sedation, constipation, nausea, and respiratory depression.[27]

While opioids are effective in the management of dyspnea, they may pose a risk of respiratory depression in patients receiving high doses or those with opioid sensitivity.[28] Respiratory depression manifests as a respiratory rate of <8–10 breaths per minute, hypoventilation, a significant drop in oxygen saturation, and hypercapnia. Therefore, regular

respiratory assessment is essential in patients receiving opioid therapy. This assessment can be performed as follows:

- **For low-risk patients:** Monitoring respiratory rate and pulse oximetry may be sufficient.
- **For moderate-to-high-risk patients:** Capnography (end-tidal CO_2 monitoring) can be used for early detection of hypoventilation.

In cases of opioid-induced respiratory depression, opioid antagonists such as naloxone may be administered. However, naloxone reverses all opioid effects, necessitating careful dose titration, particularly in palliative care patients.[29] The recommended naloxone administration doses are as follows:

- **Mild-to-moderate respiratory depression:** 0.04 mg IV slow infusion, titrated every 2–3 minutes as needed.
- **Severe opioid toxicity:** 0.1–0.2 mg IV, repeated every 2–3 minutes as necessary until the patient stabilizes.
- **Alternative administration:** 0.4 mg IM/SC.
- **Low-dose infusion (0.25–1 mcg/kg/hour):** Preferred to reverse respiratory depression without completely eliminating opioid analgesia.

Preventive strategies are crucial for enhancing the safety of opioid therapy in patients at risk of respiratory depression. Initiating treatment with low opioid doses and gradually titrating the dose is recommended. Additionally, selecting opioids with a lower respiratory depressant effect rather than those with high sedative potency may reduce the risk. Opioid rotation can be considered as an alternative strategy in patients who develop tolerance or experience adverse effects. Furthermore, multimodal analgesia strategies should be adopted whenever possible to minimize naloxone requirements, integrating non-opioid analgesics into the treatment plan.

The major side effects of opioids and their management protocols are presented in Table 2.

Table 2. Most common side effects of opioids and their management

Side effect	Prevention/management strategy
Constipation	Regular use of laxatives (lactulose, senna, macrogols). Agents that enhance peristalsis are preferred.
Nausea/vomiting	Metoclopramide (10 mg, three times daily) or ondansetron (4–8 mg, twice daily) can be used. Nausea typically resolves within the first few days after opioid initiation.
Sedation	Dose reduction or switching to an alternative opioid may be considered. The lowest effective dose should be targeted to maintain the patient's functional capacity.
Respiratory depression	Opioid titration should be performed carefully. In cases of severe respiratory depression, naloxone (0.1–0.2 mg IV, repeated as needed) can be administered.
Pruritus	Antihistamines (diphenhydramine or hydroxyzine) may be used. Alternative opioid selection should be considered if necessary.
Urinary retention	Dose reduction or catheterization may be considered if required.

Although morphine is the most commonly used opioid, alternatives such as fentanyl, oxycodone, hydromorphone, and methadone can also be considered.[30,31]

Use of Methadone in Dyspnea Management

Methadone is an opioid with unique pharmacological properties that can be used as an alternative in dyspnea management. In addition to acting as a μ-opioid receptor agonist like conventional opioids, it also functions as an N-methyl-D-aspartate (NMDA) receptor antagonist and a serotonin-norepinephrine reuptake inhibitor.[32]

Advantages of Methadone[33]

Use in opioid rotation: Methadone can be considered an alternative for patients who do not achieve adequate symptomatic relief with other opioids.

Reduction of opioid tolerance: Due to its NMDA receptor antagonism, methadone may provide efficacy at lower doses in patients who have developed opioid tolerance.

Effects on neuropathic pain and dyspnea: NMDA receptor blockade can reduce neuropathic pain and opioid-induced hyperalgesia, which may help alleviate dyspnea perception in chronic illnesses.

Risk of respiratory suppression: Compared to morphine, methadone may cause less respiratory depression; however, due to its long half-life, careful dose titration is required.

The dosage and administration of methadone should be carefully tailored to the patient's opioid tolerance and clinical condition. For opioid-naïve patients, the recommended starting dose is 2.5 mg orally every 8–12 hours. In cases requiring opioid rotation, when transitioning from morphine to methadone, the morphine equivalent dose should be calculated at 10–20% of the morphine dose, with careful titration. Due to methadone's long half-life, dose adjustments should not be made sooner than 5–7 days to prevent cumulative effects and minimize adverse reactions.

There are several key factors to consider when using methadone. First, due to the risk of cumulative effects, dose titration should be conducted cautiously, and sudden dose increases should be avoided. Methadone is known to prolong the QT interval and may lead to cardiac arrhythmias; therefore, ECG monitoring is recommended, especially during long-term use. Additionally, potential drug interactions with other sedative medications should be considered, and patients should be closely monitored. These precautions are essential for ensuring the safe and effective use of methadone in dyspnea management.

Benzodiazepines

These can be used to reduce anxiety associated with dyspnea. Anxiety can contribute to the exacerbation of dyspnea symptoms, and in such cases, managing anxiety can help alleviate dyspnea. Benzodiazepines are often used as supportive therapy in patients experiencing dyspnea accompanied by anxiety.[34] However, in the absence of an anxiety component, benzodiazepines are not recommended as a routine treatment strategy for dyspnea management.[35]

Glucocorticoids

Corticosteroids are one of the pharmacological agents frequently used in palliative care for managing dyspnea in cancer patients. They can improve respiratory function by reducing inflammation, particularly in conditions such as malignant airway obstruction, lymphangitic carcinomatosis, pulmonary inflammation, and radiation pneumonitis.[24] The anti-inflammatory and membrane-stabilizing effects of corticosteroids contribute to the alleviation of dyspnea symptoms by reducing airway edema and mucosal inflammation. In clinical practice, one of the most commonly used agents is dexamethasone, which is typically administered at a dose of 4–8 mg/day. However, long-term use of corticosteroids can lead to side effects such as hyperglycemia, muscle weakness, and immunosuppression, necessitating careful patient selection and individualized dose adjustments. Although current evidence on the effectiveness of corticosteroids in dyspnea management is limited, short-term use in selected patient groups has been reported to provide symptomatic relief.[36] Therefore, corticosteroid therapy is considered a supportive option that should be carefully evaluated in palliative care patients.

Oxygen Therapy

Oxygen therapy is an essential treatment modality used to alleviate dyspnea and potentially prolong survival in hypoxemic patients.[18] The effectiveness of long-term oxygen therapy (LTOT) varies depending on the underlying disease and the degree of hypoxemia. In COPD, LTOT is the only treatment that has been shown to improve survival in patients with a resting $PaO_2 \leq 55$ mmHg or $SaO_2 \leq 88\%$.[37] However, the efficacy of oxygen therapy in managing dyspnea in non-hypoxemic patients remains limited. Therefore, while oxygen therapy can provide significant benefits in hypoxemic individuals, it is important to recognize that unnecessary oxygen administration in normoxemic patients has minimal impact.[38]

Limitations of Noninvasive Ventilation in Palliative Use

Noninvasive ventilation (NIV) is widely used in clinical settings outside of palliative care, particularly for the management of hypercapnic respiratory failure. In patients with hypercapnic respiratory failure ($PaCO_2$ >45 mmHg, pH <7.35) during COPD exacerbations, NIV reduces the workload of the respiratory muscles, decreasing the need for mechanical ventilation and reducing mortality.[39]

Respiratory distress is commonly observed in individuals with terminal or progressive diseases, such as cancer, advanced COPD, amyotrophic lateral sclerosis, and IPF.[40,41] In these complex clinical scenarios, NIV may be preferred to provide respiratory support without resorting to invasive methods like intubation or invasive mechanical ventilation.[42] NIV involves the application of positive pressure ventilation through noninvasive interfaces, such as nasal masks, facial masks, or nasal plugs, instead of invasive airway devices like endotracheal tubes or tracheostomies.[43] The 2017 guidelines issued by the European Respiratory Society and the American Thoracic Society emphasize the support for palliative use of NIV in dyspnea patients with terminal cancer and other advanced diseases.[44] Accordingly, NIV is recommended as a palliative intervention in patients experiencing severe dyspnea who prioritize comfort-focused measures over aggressive life-prolonging treatments.[45] However, further evidence is needed to establish the effectiveness and clinical benefits of NIV in this patient population.

Non-Pharmacological Methods

- **Respiratory therapy:** Patients can be taught breathing exercises.
- **Breathing techniques:** Diaphragmatic breathing and controlled breathing techniques may provide relief.
- **Environmental adjustments:** Proper ventilation of the patient's living space, humidity control, and appropriate positioning can help alleviate symptoms.

Dyspnea Crisis and Palliative Sedation

Dyspnea crises are characterized by sudden and severe episodes of breathlessness, often occurring in the terminal stage of life.[46] In such situations, the patient's distress can be alleviated through the use of opioids, benzodiazepines, and, if necessary, palliative sedation. Palliative sedation should be considered as an option for managing refractory symptoms.

Definition and Initiation Criteria of Palliative Sedation

Palliative sedation is the controlled reduction of a patient's consciousness to relieve refractory symptoms that cannot be managed with conventional treatments. According to the European Association for Palliative Care (EAPC) guidelines, palliative sedation should only be administered when the following criteria are met:[47]

- **Presence of refractory symptoms:** Symptoms such as pain, dyspnea, delirium, anxiety, or other distressing conditions must remain unmanageable despite all available medical and pharmacological interventions.
- **End-of-life stage:** Palliative sedation is typically indicated in the terminal phase of illness (patients with a life expectancy of days or hours).
- **Patient or surrogate consent:** In cognitively intact patients, informed consent should be obtained; in unconscious patients, legal representatives should be involved in decision-making.
- **Multidisciplinary decision-making:** The decision should be evaluated by physicians, nurses, ethics committees, and the patient's family to ensure a holistic approach.
- **No intention to hasten death:** The primary aim of palliative sedation is symptom relief, and it should not be confused with euthanasia or assisted suicide.

Pharmacological Approach

The most commonly used agents in palliative sedation are benzodiazepines, neuroleptics, and barbiturates. Among these:[47]

- **Midazolam:** For mild sedation, an initial dose of 2.5 mg SC or 1.25 mg IV is recommended; for deep sedation, an initial dose of 5–10 mg SC or 2.5–5 mg IV is used. The maintenance dose is 1 mg/hour, which can be adjusted based on clinical response.
- **Phenobarbital:** Can be administered parenterally at 37.5–150 mg/day or rectally at 75–300 mg/day.

Palliative Sedation and Ethical Considerations

While palliative sedation is intended to alleviate symptoms, it may pose ethical concerns regarding its potential to hasten death. Therefore, the following aspects should be carefully considered:

- **Patient autonomy:** If the patient is conscious, they should be actively involved in decision-making; if not, the legal representatives should participate in the process.
- **End-of-life-specific application:** There is ongoing debate on whether palliative sedation should be restricted to the terminal phase. Some experts argue that sedation should focus on symptom control rather than life expectancy.
- **Multidisciplinary approach:** The decision to initiate sedation should involve ethics committees and palliative care specialists to ensure optimal patient care.

In conclusion, for palliative sedation to be implemented effectively and ethically, the patient's individual needs should be considered, the treatment process should be managed by a multidisciplinary team, and comprehensive information about the procedure should be provided to the patient and their family.

CONCLUSION

Dyspnea is a common symptom in palliative care patients that requires effective management. While current treatment approaches play a significant role in symptom control, several aspects require further investigation. The long-term efficacy and side effect profile of opioids, the potential benefits of methadone in dyspnea management, and the impact of long-term oxygen therapy on survival and quality of life need to be more clearly defined. Additionally, more comprehensive studies are required on patient selection criteria and the ethical aspects of palliative sedation. Future research will contribute to the development of more effective and patient-centered approaches in dyspnea management.

ETHICAL DECLARATIONS

Referee Evaluation Process

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Author Contributions

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

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Case Report

MEDICINE PALLIATIVE CARE

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Desmoid-type fibromatosis in the puerperium: a case report with pelvic exenteration

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ABSTRACT

Desmoid-type fibromatosis (DF) is a rare, locally aggressive soft tissue tumor with no metastatic potential but a high recurrence rate. We present the case of a 28-year-old postpartum woman who developed a rapidly enlarging pelvic mass, which was later confirmed as DF via imaging and biopsy. The initial management with chemotherapy and radiotherapy was unsuccessful, necessitating radical surgical intervention with pelvic exenteration. Given its association with hormonal changes, particularly during pregnancy and the postpartum period, DF poses significant diagnostic and therapeutic challenges. This case underscores the importance of early recognition, multidisciplinary management, and individualized treatment strategies to optimize patient outcomes.

Keywords: Desmoid fibromatosis, postpartum period, pelvic exenteration

INTRODUCTION

Desmoid-type fibromatosis (DF) is an uncommon soft tissue tumor with locally invasive growth, but no potential for distant metastasis. It accounts for approximately 0.03% of all neoplasms and exhibits a predilection for young women, particularly in hormonally influenced states such as pregnancy and puerperium.[1,2] The WHO classification of DF as an intermediate tumor reflects its high propensity for local recurrence despite complete surgical excision.[3]

The etiology of DF remains incompletely understood, although hormonal factors and genetic predispositions have been implicated. It frequently arises in association with familial adenomatous polyposis (FAP), but sporadic cases also occur, with mutations in CTNNB1 leading to abnormal β-catenin accumulation.[4] This mutation contributes to uncontrolled proliferation of fibroblasts, resulting in a locally aggressive tumor with unpredictable behavior.

The management of DF remains challenging owing to its high recurrence rate and variable clinical course. Although surgical resection has historically been the standard treatment, recent evidence suggests that radical excision with negative margins does not necessarily improve long-term outcomes, prompting a shift towards conservative approaches such as active surveillance or systemic therapy.[5,6] Given its potential for local progression, DF requires a multidisciplinary approach tailored to each patient's clinical presentation and treatment response. We aim to share our experience with a case diagnosed with DF that showed rapid progression in the puerperium period and resulted in pelvic exenteration. The informed consent form was obtained from the patient.

CASE

A 28-year-old Turkish woman, gravida 3, para 1, presented with urinary retention and a palpable vaginal mass on postoperative day 4 following an elective cesarean section at 38+4 weeks of gestation. It was learned that the patient's prenatal course was uneventful. The 8x10 cm heterogeneous appearance detected in the first ultrasonographic evaluation was thought to be a hematoma or pelvic mass, and an exploratory laparotomy was performed in the clinic where she delivered, and a solid mass with deep fixation was revealed in the right pararectal region. Given its extent and uncertainty regarding its nature, the patient was referred to our tertiary center for further assessment.

Upon admission, a comprehensive evaluation was conducted, including imaging and laboratory workup. Transperineal ultrasonography demonstrated a dense solid mass measuring 11 cm in diameter, compressing the vagina. Emergency computed tomography showed a mass approximately 10 cm in diameter associated with the uterus within the pelvic

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bone borders (Figure 1). Contrast-enhanced pelvic magnetic resonance imaging revealed a large heterogeneous tumor originating from the retrorectal space, extending into the pelvic floor (Figure 2). Laboratory results, including tumor markers (CA 125, CA 19-9, CEA, AFP), were unremarkable.

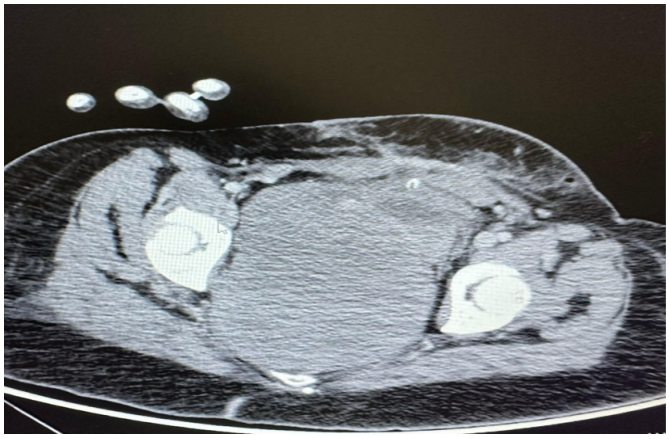

Figure 1. Heterogeneous pelvic mass with uterus within the pelvic bone borders on computed tomography

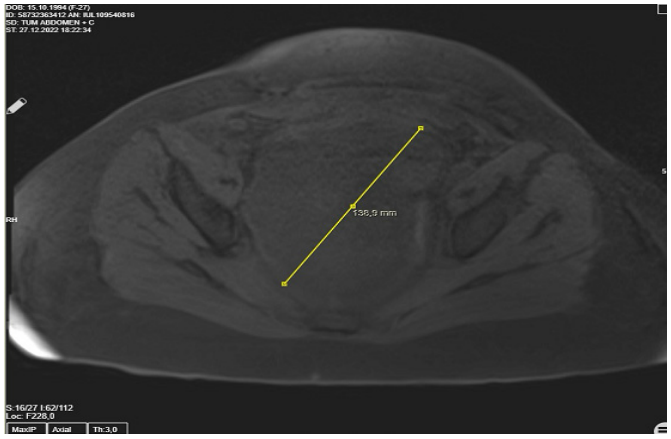

Figure 2. Magnetic resonance imaging showing a large heterogeneous pelvic mass (138×120 mm) compressing adjacent structures

A biopsy confirmed desmoid-type fibromatosis (DF) with immunohistochemical positivity for beta-catenin, vimentin, and caldesmon, raising concerns for an aggressive clinical course. The case was discussed at a multidisciplinary tumor board, and initial treatment included three cycles of chemotherapy and radiotherapy to reduce tumor burden before definitive surgery.

Despite chemotherapy, follow-up imaging showed progressive tumor growth, reaching 18x12 cm with extensive pelvic involvement. Given the tumor's aggressive nature and encroachment on adjacent structures, pelvic exenteration was deemed necessary.

On postoperative day 32, a multidisciplinary surgical team comprising general surgeons, gynecologists, and urologists performed a pelvic exenteration. A median incision was made, and upon exploration, the tumor was found infiltrating the uterus, bladder, and rectum, extending to the pelvic sidewalls. Complete en bloc resection was infeasible without significant morbidity; thus, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, total cystectomy, bilateral ureterostomy, terminal ileostomy, and abdominoperineal resection were performed.

Pathological analysis confirmed extensive desmoid fibromatosis infiltration into the bladder wall, pelvic floor, and rectum, with reactive lymphadenopathy. The patient was admitted to the intensive care unit postoperatively, requiring ventilatory support. On postoperative day 4, she developed right lower limb weakness due to obturator nerve involvement. She was initiated on physiotherapy and stoma care education before discharge.

DISCUSSION

The management of desmoid fibromatosis remains a subject of ongoing debate, with treatment strategies evolving based on the emerging clinical evidence. While surgical resection has been the mainstay of therapy, studies indicate that aggressive surgery does not necessarily reduce the risk of recurrence, leading to an increased emphasis on non-surgical treatment options, such as hormonal therapy, chemotherapy, and targeted agents.[7,8] In this case, despite the initial chemotherapy and radiotherapy, tumor progression necessitated an extensive surgical approach.

The high recurrence rate associated with DF further complicates its management. Local recurrence is frequently observed even after complete excision, particularly in cases of hormone-driven growth.[4,9] The unpredictable nature of DF necessitates a case-by-case approach to balance the risks and benefits of surgery with non-invasive management strategies.

CONCLUSION

This case highlights the importance of a multidisciplinary approach in DF treatment, particularly in hormonally influenced cases, such as those occurring in the puerperium. The integration of gynecologists, oncologists, and surgical specialists allows for comprehensive decision-making, ultimately leading to favorable surgical outcomes. Further research is needed to refine treatment algorithms, incorporate molecular and genetic insights to guide individualized therapy, and improve long-term prognosis.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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

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