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Inflammatory Biomarkers and Clinical Course in Deep Neck Infections: Role of Comorbidities and Etiology

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ABSTRACT

Objective: Deep neck infections (DNI) may present a complex clinical picture depending on etiological factors and comorbidities. The effects of these predisposing factors on biomarkers – systemic inflammatory response index, pan-immune-inflammation value, neutrophil-to-lymphocyte-to-platelet ratio, C-reactive protein–albumin–lymphocyte index (CALLY index), and hemoglobin–albumin–lymphocyte and platelet score (HALP score) – and their relationship with the disease course were evaluated.

Materials and Methods: This retrospective cohort study evaluated patients hospitalized with DNI. Demographic, clinical, and laboratory data were recorded and biomarker values calculated. Patients were grouped by infection source and comorbidities into Group A (fewer than two risk factors) and Group B (two or more). They were also classified by treatment as medical (Group 1) or surgical drainage (Group 2). Biomarkers and laboratory parameters were compared between groups, and their association with disease course was assessed.

Results: Among 82 patients, demographic features and treatment distribution were similar across groups. Group 2 (surgical drainage) had longer hospital stays (p=0.003) and lower hemoglobin (p=0.013) than Group 1. Lymphocyte counts were lower in Group B and higher in Group 2 (p=0.023, p=0.050). Group B showed reduced CALLY index and HALP score (p≤0.001), while other biomarkers were comparable. CALLY index had high sensitivity (94.9%), and HALP score showed high specificity (74.4%).

Conclusion: The coexistence of infectious sources and systemic comorbidities significantly affects the clinical trajectory and therapeutic strategies in DNI. Accordingly, biomarkers such as the CALLY index and HALP score serve as valuable tools for predicting their influence on disease progression.

Keywords: Biomarker, C-reactive protein–albumin–lymphocyte index, Deep neck infection, Hemoglobin –albumin–lymphocyte and platelet score

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INTRODUCTION

A deep neck infection (DNI) is a serious and potentially life-threatening condition that involves an infection of the deep fascial spaces of the neck. Bacteria can cause these infections, and they often arise from the spread of an infection from another area in the head or neck, such as the tonsils, teeth, salivary glands, or lymph nodes.[1] Such infections have the potential to result in significant complications, including airway obstruction and mediastinitis, which require prompt medical intervention. The management of DNIs typically involves empirical antibiotic therapy, followed by surgical incision and drainage if necessary.[1,2] The most common cause of DNIs is dental infection, particularly those involving chronic problem teeth.[1-3] Older adults, particularly those with diabetes and elevated blood glucose levels, as well as patients with chronic kidney disease, are often at increased risk of more severe disease progression and poorer prognoses due to underlying immune system dysfunction.[4,5]

Empirical intravenous antibiotics (β-lactamase-resistant β-lactam antibiotics, the third-generation cephalosporin antibiotics, metronidazole, and clindamycin) were administered before the culture results were available, then the antibiotic regimen was modified based on the culture and sensitivity results.[1,6] In cases where antibiotics prove ineffective or in instances of airway obstruction, incision and drainage are crucial.[7] New models are being developed to predict outcomes based on factors such as serum creatinine levels and the presence of mediastinitis.[8] The mortality risk is increased in cases where there are multiple infected sites, renal insufficiency, and advanced age.[7,8] While DNIs are severe, timely diagnosis and treatment can significantly improve outcomes. However, the presence of comorbidities and delayed treatment can lead to life-threatening complications, underscoring the importance of early intervention and comprehensive care strategies.[4-8]

Biomarkers such as the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) have been the subject of investigation with a view to establishing their prognostic value in DNIs. These biomarkers can assist in the prediction of complications and the guidance of treatment decisions.[9-22] CRP is a commonly used marker for assessing infection severity and has been shown to correlate with length of stay in patients with DNIs.[9] NLR is a cost-effective marker derived from routine blood tests and is comparable to CRP in predicting the length of hospitalization for DNIs.[11] In addition, NLR has been demonstrated to be a valuable tool in predicting necrotizing fasciitis and systemic involvement in DNIs.[12] NLR value can be considered in determining the prognosis of DNI, which may develop as a complication, especially in the early stages of acute bacterial tonsillitis.[11,20] CRP, NLR, and SII have been reported as effective biomarkers in the early diagnosis of deep neck abscess or necrotizing soft-tissue infection that may develop depending on the severity of odontogenic infections.[17] Biomarkers such as the SII and systemic inflammation response index (SIRI), which are derived from laboratory parameters including CRP and NLR, contribute to the optimization of DNI management by complementing clinical and radiological assessments.[16-18] Notably, the SII index has shown high diagnostic accuracy in predicting DNI-related complications.[16] Nutritional deficiencies and immunological impairments associated with chronic comorbid conditions are anticipated to significantly influence both the therapeutic trajectory and clinical outcomes of patients diagnosed with DNIs. Given the multifactorial etiology of DNI, including infection sources and the impact of systemic comorbidities, comprehensive evaluation through emerging biomarkers, novel indices, and advanced scoring systems is of considerable clinical relevance. There are not enough studies investigating the relationship between SIRI, pan-immune-inflammation value (PIV), neutrophil-to-lymphocyte-to-platelet ratio (NLPR), C-reactive protein–albumin–lymphocyte Index (CALLY index), hemoglobin, albumin, lymphocyte, and platelet score (HALP score), and DNI. Therefore, in our study, we aimed to evaluate the impact of comorbidities and infection etiology in patients with DNI on inflammatory parameters such as SIRI, SII, PIV, NLPR, CALLY index, and HALP score; as well as the relationship between changes in these biomarkers, and the clinical course of DNI patients.

MATERIALS AND METHODS

In this retrospective cohort study, cases of DNI diagnosed by otorhinolaryngology specialists and managed through inpatient hospitalization, follow-up, and treatment were evaluated. This study includes patients who presented to the emergency department or otorhinolaryngology clinic between January 1, 2019, and June 31, 2024, and were confirmed to have a diagnosis of DNI. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and received approval from the Local Ethics Committee (Approval No: 16/9, Date: October 24, 2024).

Patients requiring hospitalization due to DNI were included in the study. The decision for hospitalization was made for patients presenting with prominent clinical findings such as erythema, swelling, heat sensation in the head-and-neck region, trismus, along with difficulty in eating and/or breathing, and a need for intravenous antibiotic therapy. Patients were excluded from the study if they were under 18 years of age, had a history of head and neck surgery or penetrating infected wounds, had been diagnosed with head and neck cancer, or had previously undergone radiotherapy or chemotherapy. Further exclusion criteria included the presence of tumors in other anatomical regions (including both solid and hemato-

logical malignancies), immunosuppressive disease, abscesses resulting from foreign bodies, resistance to treatment with multiple intravenous antibiotics, and incomplete medical records.

Demographic data, including age, gender, length of hospital stay, and details of medical, interventional, or surgical treatments administered to the patients included in the study, were recorded. In addition, hemogram and biochemical parameters measured at the time of hospital admission, such as hemoglobin (Hb) levels (g/dL), white blood cell (WBC) count and its subtypes (10^3/mm^3), platelet (PLT) count (10^3/mm^3), albumin (g/L), and CRP levels (mg/L), were collected. Using these hematological and biochemical laboratory data, the biomarkers evaluated in the study were calculated.

The calculated parameters included SII, SIRI, PIV, and NLPR values, as well as the CALLY index and HALP score. The SII was calculated by multiplying the peripheral platelet count by the neutrophil count and dividing the result by the lymphocyte count. SIRI was calculated using the formula in which the monocyte count is multiplied by the neutrophil count, and the resulting value is then divided by the lymphocyte count. The PIV is calculated by multiplying the neutrophil count, monocyte count, and platelet count, and then dividing the result by the lymphocyte count. The NLPR was calculated by dividing the neutrophil count by the product of the lymphocyte count and the platelet count. The CALLY index is determined by multiplying the serum albumin concentration by the peripheral lymphocyte count, followed by division of the resulting product by the CRP level scaled by a factor of ten. This composite metric integrates nutritional and inflammatory parameters to provide prognostic insight in various clinical settings. The HALP score was calculated by multiplying the Hb level by the albumin concentration and the lymphocyte count, and then dividing the result by the platelet count.

Patients were stratified based on the presence of infectious sources and comorbidities associated with DNI. Among the DNI cases included in this study, identifiable etiological sources comprised odontogenic infections (e.g., dental abscesses and periodontitis), tonsillitis and peritonsillar abscesses, pharyngeal infections, salivary gland obstruction or infection, lymphadenitis, infected congenital neck cysts (including branchial cleft cysts and thyroglossal duct cysts), and skin or soft-tissue infections, particularly cellulitis extending into the deep neck spaces. The comorbidities assessed in this cohort included hypertension, diabetes mellitus, cardiopathy, anemia, endocrinopathies (excluding diabetes), chronic kidney disease, alcohol and substance abuse, chronic liver disease, and chronic obstructive pulmonary disease. Regardless of the presence or absence of a defined infectious source, two distinct cohorts were established to evaluate relevant biomarkers. A cohort was formed comprising patients who presented with two or more infectious sources or comorbidities (Group B); those with fewer than two of these risk factors were categorized into a distinct group (Group A). The impact of multiple concurrent etiological and comorbid risk factors on the severity of inflammation and infection was comparatively analyzed through biomarker profiling. In addition to medical therapy (Group 1), patients enrolled in the study were further classified according to their requirement for either ultrasound-guided drainage or incisional open surgical drainage (Group 2). The demographic data of the patients, length of hospital stay, laboratory parameters, and evaluated biomarkers were compared between Groups A and B, as well as between Groups 1 and 2. To assess the relationship between the CALLY index and HALP score with hospital stay duration, the length of hospital stay was categorized into short stay (SS) (<7 days) and extended stay (LS) (≥7 days).

Statistical Analysis

The statistical analyses were conducted using the Statistical Package for Social Sciences for Windows 27.0 program. Categorical data were defined as percentages and frequencies. The numeric data were determined, and a distribution analysis was performed. Data sets that conformed to a normal distribution were defined as mean±standard deviation (SD). For data sets that did not conform to a normal distribution, the median and interquartile range (IQR) were defined. The Chi-square test was employed to ascertain the relationship between categorical data. The analysis of numeric tests that followed a normal distribution was conducted using parametric tests (t-test and analysis of variance [ANOVA]); nonparametric tests were used in the analysis of numeric tests that did not follow a normal distribution. Subsequent comparisons were made using paired t-tests and ANOVA. The receiver operating characteristic test was employed to calculate the effect power of the dependent variable. A threshold value was determined, and the sensitivity and specificity were subsequently calculated based on this value. Statistical findings with a p-value below 0.05 were considered to be statistically significant.

RESULTS

A total of 82 patients were included in the analysis, having met the pre-established inclusion criteria. There was no significant difference in gender distribution or age across the groups ($p>0.05$). Similarly, there was no significant difference in the medical therapy and drainage rates between Group A and B, Group 1 and 2 ($p>0.05$). However, patients who underwent drainage had a significantly longer treatment time ($p=0.003$) (Table 1). Hb levels were significantly lower in Group 2 compared to Group 1 ($p=0.013$). Regarding lymphocyte counts, statistically significant differences were observed both between Group B and Group A ($p=0.023$), and between Group

Table 1. Baseline patient characteristics and initial clinical findings in patients with and without a number of risk factors and drainage of a deep neck infection

	Number of etiological and comorbid disease factors			Drainage required		
	Group A <2 (n=43)	Group B ≥2 (n=39)	p	Group 1 No (31)	Group 2 Yes (51)	p
Gender, Female (n, %)	12 (27.9)	12 (30.8)	0.184	9 (29)	15 (29.4)	0.197
Age (mean±SD)	42.81±21.63	42.71±18.64	0.440	42.54±19.08	42.9±20.95	0.356
Treatment (n, %)						
Observation	17 (39.5)	14 (35.9)	0.575	31 (100)		
Incisional drainage	19 (44.2)	20 (51.3)			39 (76.5)	
Interventional drainage	7 (16.3)	5 (12.8)			12 (23.5)	
Lenght of hospital stay, day (mean±SD)	7.67±5.22	9.48±6.06	0.139	6.13±3	9.98±6.42	0.003

2 and Group 1 (p=0.050). Lymphocyte levels were lower in Group B, which included patients with two or more infectious sources or comorbidities. Conversely, patients who underwent surgical or interventional drainage (Group 2) exhibited higher lymphocyte counts.

As shown in Table 2, no statistically significant differences were observed between Group B, which included patients with two or more infectious sources or comorbidities, and Group A in terms of WBC count, platelet count, neutrophil, monocyte, and eosinophil levels, as well as albumin and CRP values (p>0.05). Similarly, no statistically significant differences were found in these parameters between patients who underwent surgical or interventional drainage (Group 2) and those who were managed with medical therapy (p>0.05) (Table 2). Accordingly, the results of the biomarkers calculated using the parameters as presented in Table 2 and Table 3. Similar to the laboratory parameters, as shown in Table 3, no statistically significant differences were found in the biomarker values we evaluated in our study, namely SII, SIRI, PIV, and NLPR, between Group A and Group B (p>0.05), or between Group 1 and Group 2 (p>0.05) (Table 3). Likewise, no statistically significant differences were observed in the CALLY index and HALP score between patients who underwent surgical or interventional drainage (Group 2) and those who were treated with medical therapy (Group 1) (p>0.05) (Table 3). Statistically significant

Table 2. Comparison of laboratory findings in patients with deep neck infections, classified according to the number of etiological and comorbid disease factors, and the need for surgical or interventional drainage

	Number of etiological and comorbid dis-ease factors			Drainage required		
	Group A <2 (n=43)	Group B ≥2 (n=39)	p	Group 1 No (31)	Group 2 Yes (51)	p
White blood cell (mean±SD)	15.76±4.77	14.81±5.19	0.697	15.12±4.48	15.41±5.29	0.222
Hemoglobine (mean±SD)	13.3±1.37	13.51±1.59	0.503	13.78±1.1	13.17±1.63	0.013
Platelet (mean±SD)	307.58±104.03	293.92±99.83	0.669	293.12±94.81	305.92±106.23	0.838
Neutrophil (mean±SD)	12.13±4.78	11.79±4.95	0.843	11.71±4.27	12.12±5.19	0.147
Lymphocyte (mean±SD)	2.23±0.68	1.56±0.69	0.023	1.86±0.68	1.93±0.98	0.050
Monocyte (median. IQR)	1.27(0.89)	1.19 (1.12)	0.311	1.23 (0.64)	1.27 (1.16)	0.253
Eosinophile (median. IQR)	0.08 (0.22)	0.08 (0.14)	0.727	0.07 (0.1)	0.13 (0.23)	0.324
CRP (mean±SD)	130.9±110.5	184.58±117.05	0.486	160.29±107.69	154.1±121.97	0.671
Albumine (mean±SD)	36.9±8.27	30.53±7.80	0.888	35.38±8.40	32.95±8.69	0.913

CRP: C-Reaktif Protein; SD: Standard Deviation; IQR: Interquartile Range.

Table 3. Biomarker comparison in patients with deep neck infections, grouped by the number of etiological and comorbid conditions, and by the presence or absence of surgical or interventional drainage requirement

	Number of etiological and comorbid disease factors			Drainage required		
	Group A <2 (n=43)	Group B ≥2 (n=39)	p	Group 1 No (31)	Group 2 Yes (51)	p
SII (median. IQR)	1396.18 (1254.27)	1979.08 (3687.78)	0.078	1642.75 (1076.12)	1897.84 (2495.11)	0.563
SIRI (median. IQR)	7.33 (14.92)	9.57 (12.81)	0.770	5.96 (8.92)	9.57 (26.91)	0.142
PIV (median. IQR)	1930.88 (4828.58)	2200.89 (4131.17)	0.930	1854.47 (2108.97)	2479.56 (7237.72)	0.153
NLPR (median. IQR)	0.183 (0.02)	0.022 (0.03)	0.072	0.02 (0.02)	0.022 (0.03)	0.749
CALLY (median. IQR)	0.734 (2.19)	0.273 (0.58)	0.001	0.4 (0.95)	0.46 (1.42)	0.860
Hemoglobin –albumin–lymphocyte and platelet (me-dian. IQR)	3.40 (2.38)	1.82 (2.04)	<0.001	3.14 (2.80)	2.43 (2.32)	0.130

CALLY: C-Reactive Protein–Albumin–Lymphocyte Index; IQR: Interquartile Range; SIRI: Systemic Inflammatory Response Index; SII: Systemic Immuno-Inflammation Index; PIV: Pan-Immune Inflammation Value; NLPR: Neu-trophil–lymphocyte–Platelet Ratio.

Table 4. Receiver operating characteristic analysis according to risk factor count

	Area under the curve±SD	p	Cut-off	Sensitivity	Specificity
C-reactive protein–albumin–lymphocyte index	0.710±0.057	<0.001	1.676	94.9	37.2
Hemoglobin–albumin–lymphocyte and platelet score	0.715±0.057	<0.001	2.286	61.5	74.4

differences were identified in both the CALLY index and HALP score between Group A and Group B (p≤0.001), as presented in Table 3. Importantly, patients in Group B, characterized by the presence of two or more infectious foci or underlying comorbid conditions, exhibited markedly lower values in both indices compared to those in Group A.

A comparative analysis of the CALLY index and HALP score based on their respective area under the curve (AUC)±SD values demonstrates that the CALLY index yields an AUC of 0.710±0.057, whereas the HALP score presents a slightly higher AUC of 0.715±0.057 (p<0.001). Sensitivity analysis reveals that the CALLY index exhibits superior sensitivity (94.9%) compared to the HALP score (61.5%), indicating greater efficacy in detecting true positive cases. Conversely, specificity, reflecting the ability to correctly identify actual negatives, is higher for the HALP score (74.4%) than for the CALLY index (37.2%), suggesting that HALP is more reliable in excluding false positives. These findings are detailed in Table 4 and Figure 1. The specific clinical or diagnostic context should guide the choice between the CALLY index and HALP score. In situations where minimizing the risk of overlooking actual positive cases is crit-

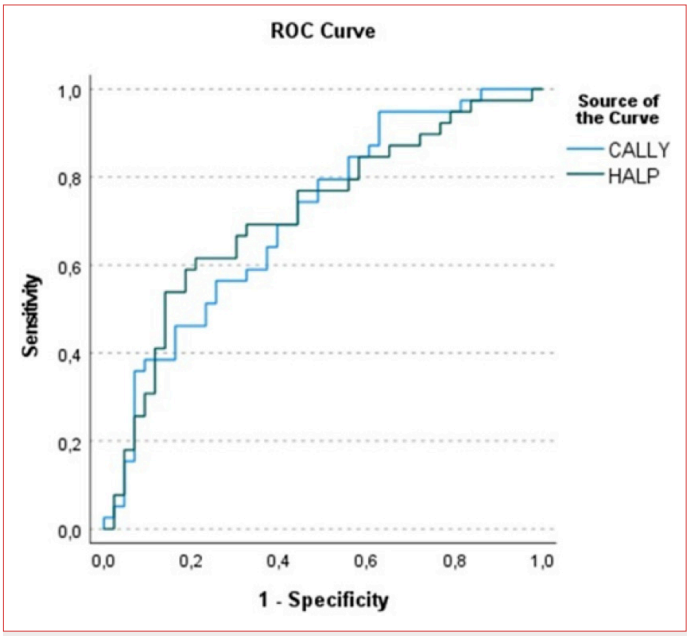

Figure 1. Receiver operating characteristic curves of parameters to predict DNI in number of risk factors group.

ical, such as in early detection or screening protocols, CALLY, with its higher sensitivity, may be the more appropriate tool. Conversely, in settings where the reduction of false-positive results is prioritized – such as in confirmatory diagnostics or resource-limited environments – HALP, owing to its superior specificity, may offer greater clinical utility.

In the assessment based on patients' length of stay in hospital, the median CALLY index value was found to be 0.72 (1.70) for patients with a short length of stay and 0.29 (0.71) for patients with an extended length of stay (p=0.006). A similar assessment was performed within the HALP score regarding length of hospital stay, but no statistically significant result was obtained (p=0.400).

DISCUSSION

In DNIs, the prevention of life-threatening complications such as sepsis, mediastinitis, and airway obstruction is the primary goal of the follow-up and treatment process. Therefore, being able to predict whether potential sources of infection involved in the etiology will cause DNI development and, if DNI develops, whether it will lead to these complications is of critical importance in clinical management. Studies exist on the presence of an etiological source of infection, patients' comorbidities, and the effects of these risk factors on the clinical course of DNI and the development of complications.[2-4,8, 9,16,21,23-25] These studies report that the presence of an odontogenic infection source, impaired blood sugar regulation due to diabetes, abnormalities in WBC and Hb levels, low blood albumin levels, high creatinine levels, and the presence of cardiopulmonary disease affect the clinical course and severity of infection and the development of complications in DNI patients.[8,9,21,23,25]

In the literature, the relationship between basic laboratory parameters such as WBC, neutrophil, platelet, mean platelet volume, CRP, ESR, and serum creatinine levels and the development and clinical course of DNI has been evaluated.[8,13,14,16,21,22] Furthermore, inflammatory biomarkers such as NLR, PLR, SII, and SIRI have also been similarly investigated in DNI patients.[9-12,14-20,22] These studies indicated that classical laboratory parameters and inflammatory biomarkers could be used as critical predictive markers in the clinical management of DNI and in terms of hospitalization duration, the need for surgical drainage, and the development of complications. Unlike the studies in the literature, new biomarkers such as the CALLY index and HALP score, which we believe can more reliably and comprehensively assess the clinical course of infection, complication risk, and treatment planning in DNI patients in relation to the source of infection and comorbidity, have been examined as predictive markers.

In DNI patients, the correlation of each accompanying disease with the clinical course can be assessed separately. However, as the number of comorbidities and additional risk factors increases, beyond the etiological cause of the infection, clinical evaluation can be performed using multivariate analyses. In clinical studies, multivariate analysis helps clarify the multifaceted nature of risk factors and their relative contribution to outcomes. Studies using multivariate models to analyze DNI prognosis and complication development evaluated large cohorts, but none of the clinical variables consistently demonstrated an independent and meaningful prognostic role.[23] This highlights the complexity and interdependence of various clinical variables contributing to DNI prognosis. Therefore, in DNI patients, cost-effective methods are needed to assess the clinical course and predict complications, independent of the infection's cause, comorbidities, and abundance of risk factors. Inflammatory biomarkers such as SII, SIRI, PIV, and NLPR, easily obtained from laboratory parameters, may be valuable. However, when albumin and Hb levels reflecting nutritional status, lymphocyte count indicating immunological status, and CRP level as an inflammation marker are evaluated with the CALLY index and HALP score, more clinically meaningful and valuable results are obtained.

In this study, it was determined that in patients with DNI, only the lymphocyte count was affected by the source of infection and accompanying comorbidities, whereas other classic laboratory parameters and inflammatory biomarkers, such as SII, SIRI, PIV, and NLPR, did not show significant change. In contrast, the CALLY index and HALP score values were influenced by the infection source and number of comorbidities, with a significant correlation between these parameters. In our study, CALLY's sensitivity was higher than HALP's, at 94.9% versus 61.5%. Selection between CALLY and HALP may depend on specific clinical or diagnostic needs. In scenarios where missing a positive case (high sensitivity) is critical, CALLY may be preferred.

The CALLY index was first defined as a highly predictive tool for stratifying patients with hepatocellular carcinoma.[26,27] It provides a comprehensive assessment of a patient's inflammatory status, nutritional condition, and immune function. Studies on the CALLY index have reported findings related to the clinical course of diseases involving not only gastrointestinal tumors but also systemic inflammatory conditions such as rheumatoid arthritis, peripheral artery disease, ischemic stroke, and sepsis.[28-31] The HALP score, defined for gastric carcinomas, also enables evaluation of disease course in relation to inflammatory status, nutritional condition, and immune function. The prognostic significance of combining preoperative HALP has been reported in gastric carcinomas.[32] HALP has also been evaluated in patients with ischemic stroke and sepsis.[33,34] Both CALLY and HALP are associated with short- and long-term adverse outcomes in sepsis. Therefore, assess-

ing patient status using CALLY and HALP may help improve sepsis prognosis. In DNIs, integrating inflammatory, nutritional, and immunological markers into clinical decision-making enhances early prognostic assessment of sepsis secondary to infection.[31,34]

The etiological source of infection and predisposing conditions from patients' comorbidities may increase the severity of the clinical course in DNI, affecting the need for surgical drainage, complication development, and hospital stay duration. No association was found between the CALLY index, HALP score, and inflammatory biomarkers with the need for surgical drainage in DNI patients. An assessment was attempted for complications in the DNI patients we followed; however, since complications occurred in only three patients (one with mediastinitis, one with necrotizing fasciitis, and one with airway obstruction), statistical evaluation of the relationship between these biomarkers and complication development was not possible. Assessment of the relationship between the length of hospital stay and the CALLY index and HALP score revealed that patients with prolonged hospitalization had lower CALLY index values. This suggests that patients with poor nutritional and immunological status and higher inflammation levels tend to remain hospitalized longer.

It should be noted that our study has certain limitations. First, the study was designed retrospectively and conducted at a single center. In addition, the sample size is relatively small, and the number of complications is insufficient for statistical evaluation. We are aware that inflammatory parameters such as the CALLY index, HALP score, SII, SIRI, and NLPR may require dynamic monitoring. In our study, assessment was based on laboratory values obtained at patients' initial presentation and during hospitalization. Therefore, we acknowledge important limitations, such as monitoring all laboratory parameters and biomarkers throughout hospitalization. It was determined that the CALLY index and HALP score were affected by the etiological cause, presence of comorbidities, and number of these predisposing conditions in DNI patients; however, their relationship with surgical drainage need and complications could not be established. To validate the predictive efficacy of biomarkers regarding DNI patients' clinical course, prospective studies with larger sample sizes and multiple centers are required.

CONCLUSION

In patients with DNI, the presence of an etiological infection source and predisposing conditions such as concomitant systemic diseases may influence the clinical course of the disease, the treatment approach, and the development of complications. The use of biomarkers to predict the effect of such a large number of interrelated and interacting predictive variables on DNI may lead to meaningful improvements in the clinical and prognostic follow-up and treatment of DNI patients. Multifactorial biomarkers such as the CALLY index and HALP score allow for the assessment of not only inflammation and immunological status but also hematological and nutritional status in complex diseases such as DNI, thereby providing insights into disease severity and progression.

DECLARATIONS

Ethics Committee Approval: The study was approved by Antalya Training and Research Hospital Ethics Committee (No: 16/9, Date: 24/10/2024).

Informed Consent: This was a retrospective study; thus, informed consent was not obtained.

Conflict of Interest: The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

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The Effect of Spinal Column Flexion on Block Quality in Spinal Anesthesia Applied in the Lateral Decubitus Position for Inguinal Hernia Surgery

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ABSTRACT

Objective: Unilateral spinal anesthesia is often preferred to reduce the hemodynamic side effects of spinal anesthesia. This study aims to examine the impact of spinal column flexion on unilateral block development and hemodynamics.

Materials and Methods: Sixty patients, aged 18–65 years, were randomly allocated into three groups. Each of the three groups was administered 12.5 mg of heavy bupivacaine through intrathecal injection. In Group 1, spinal anesthesia was administered with the patient positioned laterally, the operative side facing downward, and the legs flexed, maintaining this position for 10 min. In Group 2, spinal anesthesia was administered while the patient was positioned laterally, and they were maintained in this position with their feet aligned for 10 min. In Group 3, spinal anesthesia was administered while the patient was seated, after which the patient was promptly repositioned to the lateral position and maintained in that orientation for 10 min. Hemodynamic alterations and the levels of motor and sensory blockade were documented in the patients.

Results: Patients in Group 1 had less hypotension and bradycardia than the other groups. In terms of sensory and motor block, it was discovered that in Group 1, block developed earlier on the operative side than in the other groups, but later on the contralateral.

Conclusion: This study illustrates that spinal column flexion is a viable alternative method, offering advantages such as minimal hemodynamic impact and expedited block formation for unilateral anesthesia.

Keywords: Anesthesia unilateral, Hemodynamics, Lateral decubitus, Spinal anesthesia

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INTRODUCTION

Applications of spinal anesthesia in the lateral decubitus position, particularly in cases that are appropriately chosen, lessen the negative effects of spinal anesthesia.[1] The sympathetic block caused by spinal anesthesia reduces the preload of the heart, leading to a decrease in blood pressure.[2] When unilateral spinal anesthesia is performed, the sympathetic chain on the opposite side is less affected, allowing the resulting drop

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in blood pressure to be compensated. Many methods are used to create unilateral spinal anesthesia. In the literature, there are many studies that have attempted to create a unilateral block by testing methods such as the dose of injected local anesthetic, baricity, amount of local anesthetic, infusion rate, duration of lateral decubitus position, and the use of different types of spinal needles.[3-6] In the cerebrospinal fluid, the cauda equina can move around a lot. By pulling on nerves along the spine, spinal flexion (knee–chest position) in the supine position moves the cauda equina from a dorsal-dependent area to a ventral-nondependent area. In the lateral position, when the spinal column straightens, the cauda equina falls and moves to the dependent side. When the spinal column bends to the side, the tightened cauda equina moves to the side that is not dependent and rests in the middle of the intrathecal sac.[7-9] The gathering of the cauda equina at the midline in the flexion position may provide a potential advantage for creating a unilateral block with spinal anesthesia.

This study aimed to investigate the effects of flexing the spine in the lateral decubitus position and holding it in the knee-chest position on hemodynamics and unilateral block quality in patients who underwent spinal anesthesia. Patients suitable for unilateral spinal anesthesia who will undergo unilateral inguinal hernia surgery were selected for this study.

MATERIALS AND METHODS

This study was conducted within the Department of Anesthesiology and Reanimation at Kecioren Education and Research Hospital, with the approval of the ethics committee obtained through the Clinical Research Application Form registered under B.10.4.ISM.4.06.68.49. This study was conducted in accordance with the current principles of the Helsinki Declaration. A total of 60 patients, planned for elective unilateral inguinal hernia repair and classified as the American Society of Anesthesiologists (ASA) I-II risk group and aged 18–65, were included in the study after reading and signing the informed consent form. Patients who did not accept regional anesthesia, had an intracranial mass, lumbar deformity, respiratory or heart failure, peripheral neuropathy, and known local anesthetic allergy were not included in the study.

Patients were divided into three groups. Spinal anesthesia was performed in all three groups with intrathecal administration of 12.5 mg hyperbaric bupivacaine. In Group 1, the patients were positioned laterally with the operative side down and their legs flexed (fetal position). The local anesthetic was administered in the subarachnoid space at the L3-L4 level without barbotage within 60 s. The patients were kept in this position without changing for 10 min. In Group 2, the same position as in Group 1 was given, and a local anesthetic was administered within 60 s without performing a barbotage. After spinal anesthesia was applied in this group, the patients were kept in a lateral decubitus position with their legs straight for 10 min. In Group 3, the local anesthetic was administered within 60 s without performing a barbotage, entering the subarachnoid space at the L3-L4 interval while in a sitting position. Then, the patients were kept in a lateral decubitus position with the operation side down and legs straight for 10 min, as in Group 2. In all groups, after the 10th min, the patients were placed in the supine position and handed over to the surgical team. Bupivacaine (Heavy Marcain 0.5% 4 mL amp, AstraZeneca) was used as a local anesthetic.

The sensory and motor block levels of spinal anesthesia were assessed every 3 min during the first 10 min, every 5 min until the 30th min, and subsequently every 10 min until the 80th min. The hemodynamic indicators, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO2), were recorded every 3 min during the first 10 min and then every 5 min during the first 30 min of the operation. The level of sensory block was evaluated using a blunt-tipped needle with the "pin prick" test, and the degree of motor block was assessed using the Modified Bromage Scale (MBS). The presence of analgesia at the T10 level was considered sufficient for sensory block, and the surgery was allowed to commence. The evaluation of the sensory and motor block was conducted during the operation with the knowledge of the surgical team.

The evaluations related to the sensory and motor block were conducted according to the definitions below.

The two-segment regression time of the sensory block: The duration from the moment the highest dermatome level is first reached to the moment two dermatomes have regressed.

- Motor block onset time: The duration until a score of 1 according to the MBS is achieved after spinal anesthesia is administered.
- Sensory block onset time: The duration from the administration of spinal anesthesia until there is no pain in the lowest dermatome area.
- Sensory block termination time: The duration from the onset of the sensory block to the point where the sensory block is determined to have resolved in all dermatomes through the pin prick test.
- Motor block resolution time: The duration from the onset of the motor block until the Modified Bromage score returns to 0.
- Maximum dermatom level reached for sensory block: The maximum dermatom level reached after spinal anesthesia was measured using the "pin prick test."

When the SAB dropped more than 30% according to the control values or the OAB fell below 60 mmHg, hypotension was accepted, and rapid fluid replacement was performed. If no response was obtained within 3 min, treatment was administered with a 5 mg IV bolus of ephedrine (Efedrin HCl amp, 0.05g, 1mL, OSEL, Istanbul). The decrease in HR below 50 beats/min was evaluated as bradycardia and treated with atropine (Atropine sulfate 0.5 mg, 1 mL amp, OSEL, Istanbul) 0.5 mg IV bolus. The administered medications were recorded on the form.

Patients were monitored for side effects such as hypotension, bradycardia, nausea, vomiting, pain, shivering, restlessness, and respiratory depression throughout the operation. When the surgical procedure was completed, the patients were taken to the recovery room, and their sensory and motor block levels were recorded. Patients whose follow-up parameters in the recovery room were normal were sent to the general surgery ward. In the ward, sensory and motor block levels, the time of the first urination, the time of the first mobilization, and the time of the first analgesic administration were recorded. Patients were advised to consume 3 L of fluid for 3 days from the moment oral intake was permitted after the operation. After discharge, they were advised to contact the researchers in case of complications such as headaches, back pain, loss of strength, numbness in the legs, or inability to control urination and defecation.

Statistical Analysis

PASS 11 power analysis based on past studies of block formation times showed that a minimum sample size of 54 was needed to get about 82% power. Sixty cases were included to account for possible losses. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used to examine the data. Mean ± standard deviation, median (min–max), frequency, and percentage were used to show descriptive data. The Pearson Chi-square test was used to look at categorical factors. Visually and mathematically (Kolmogorov–Smirnov/Shapiro–Wilk tests), it was checked for normalcy. One-way ANOVA was used for variables with a normally distributed, whereas the Wilcoxon Signed-Rank test (two dependent groups) and the Kruskal–Wallis test (three independent groups) were used for variables with a non-normal distribution. The Mann–Whitney U-test with Bonferroni correction was used for pairwise comparisons after the fact. A $p<0.05$ was thought to be statistically significant.

RESULTS

A total of 60 patients were included in the study, and all were accepted for analysis. No statistically significant differences were found between the study groups in terms of age, gender, height, BMI, and ASA classification ($p>0.05$) (Table 1). "In Group 1, SBP values did not differ significantly from baseline at any measurement time ($p>0.05$). In contrast, in Group 2 and Group 3, SBP values were significantly lower than baseline starting from the 3rd min and thereafter ($p<0.05$).

Table 1. Distribution of descriptive characteristics among study groups

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	p
Age (year)	40.65±13.89	46.50±12.74	46.40±14.93	0.320*
Height (cm)	170.55±6.86	175.15±6.42	172.50±5.18	0.070*
Weight (kg)	73.70±11.70	75.20±7.68	74.05±8.27	0.870*
BMI (kg/m^2)	25.22±2.86	24.49±1.94	23.1±0.52	0.631*
Gender				
Male	16 (80.0)	17 (85.0)	17 (85.0)	0.887
Female	4 (20.0)	3 (15.0)	3 (15.0)	
American Society of Anesthesiologists				
I	12 (60.0)	7 (35.0)	6 (30.0)	0.119
II	8 (40.0)	13 (65.0)	14 (70.0)	

Continuous variables are presented as "mean±standard deviation," and gender is presented as "number (column percentage). One-Way Analysis of variance. BMI: Body Mass Index.

Regarding DBP, patients in Group 2 showed significantly lower values compared to baseline from the 6th min onward ($p<0.05$). In Group 3, DBP values were significantly lower at the 6th, 15th, 20th, 25th, and 30th min, while no significant differences were observed at the 3rd and 10th min ($p>0.05$). In Group 1, DBP values remained comparable to baseline throughout the study ($p>0.05$) (Table 2)." In Group 1, statistically significant differences in sensory block levels on the operative side were observed at the 3rd, 5th, 10th, and 80th min ($p<0.05$). No significant differences were detected at the other time points ($p>0.05$). Post-hoc pairwise comparisons revealed that the significant differences at the 3rd, 5th, and 10th min were attributable to Group 3, whereas the significant difference at the 80th min was attributable to Group 2. In the patients in Group 3, the sensory block levels on the operative side at 3, 5, and 10 min were significantly lower than those in Group 1 and Group 2, while the sensory block level on the operative side of the patients in Group 3 at 80 min was significantly higher than those in Group 1 and Group 2. When evaluating the sensory block levels between the operative side and the other side within each group of patients, in Group 1, a statistically significant difference was found at all times ($p<0.05$). Group 1 had a significantly higher sensory block level on the operative side compared to the other side at all times (Fig. 1). Among the study groups included in

Table 2. Distribution of heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and peripheral oxygen pressure at various times during the operation period among the study groups

Time	Group 1 (n=20) $\bar{X}$±S	Group 2 (n=20) $\bar{X}$±S	Group 3 (n=20) $\bar{X}$±S	p*
Heart rate (beats/min)				
Initial	85.20±13.48	84.20±12.52	88.85±10.13	0.251
3rd min	85.55±14.16	81.25±11.01	86.55±10.10	0.269
6th min	84.25±9.55	81.15±9.45	84.75±7.29	0.540
10th min	82.85±9.73	79.55±11.88#	82.25±9.55#	0.812
15th min	83.00±11.97	72.95±10.46#	78.40±10.71#	0.034[a]
20th min	79.85±10.11	72.75±10.88#	75.20±8.72#	0.147
25th min	78.20±6.94#	73.75±10.34#	75.60±8.49#	0.484
30th min	77.55±6.12#	72.95±12.73#	76.00±9.62#	0.400
p-value**	0.052	<0.001	<0.001	
SBP (mmHg)				
Initial	125.05±15.90	131.65±12.68	132.70±16.66	0.117
3rd min	120.70±14.47	126.50±15.70#	126.25±15.54#	0.508
6th min	118.80±15.99	122.40±10.98#	122.15±16.07#	0.812
10th min	120.20±18.25	121.50±10.53#	123.50±12.02#	0.806
15th min	121.65±11.52	120.25±10.28#	120.65±10.51#	0.971
20th min	119.55±15.16	119.50±11.04#	119.50±9.47#	0.766
25th min	118.90±11.90	120.00±9.45#	120.80±8.62#	0.805
30th min	118.70±10.33	119.40±12.97#	118.05±12.65#	0.983
p-value**	0.351	<0.001	<0.001	
DBP (mmHg)				
Initial	75.70±11.72	76.70±10.46	81.15±13.89	0.205
3rd min	74.25±12.45	75.95±11.68	77.85±13.11	0.317
6th min	71.35±11.57	73.15±11.85#	74.05±14.35#	0.710
10th min	70.60±13.01	72.35±9.11#	77.60±11.29	0.129
15th min	72.85±7.61	68.40±8.33#	74.70±9.36#	0.099
20th min	70.95±9.17	70.30±8.96#	75.00±9.23#	0.191
25th min	71.55±10.73	72.00±10.02#	74.85±10.82#	0.589
30th min	71.60±9.40	68.90±8.30#	73.05±9.47#	0.280
p-value**	0.154	<0.001	0.002	
MAP (mmHg)				
Initial	91.60±12.35	91.60±9.89	98.15±13.75	0.172
3rd min	89.75±11.81	94.90±13.17	95.15±12.88	0.224
6th min	89.20±11.87	91.00±11.76	90.20±13.69#	0.971
10th min	88.25±12.77	89.25±11.91	91.60±10.09#	0.578
15th min	89.20±8.99	86.85±9.09#	87.55±9.74#	0.464
20th min	85.75±11.99	86.75±9.26#	87.00±9.35#	0.923
25th min	86.25±11.23	86.90±8.80#	88.10±10.79#	0.864
30th min	84.50±11.51	85.70±10.57#	86.35±11.67#	0.764
p-value**	0.018	0.001	<0.001	

*Kruskal–Wallis Test, **Friedman Test. Significant difference between "Group 1" and "Group 2" # compared to baseline value p<0.05. $\bar{X}$: Mean, S: Standard Deviation, HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure.

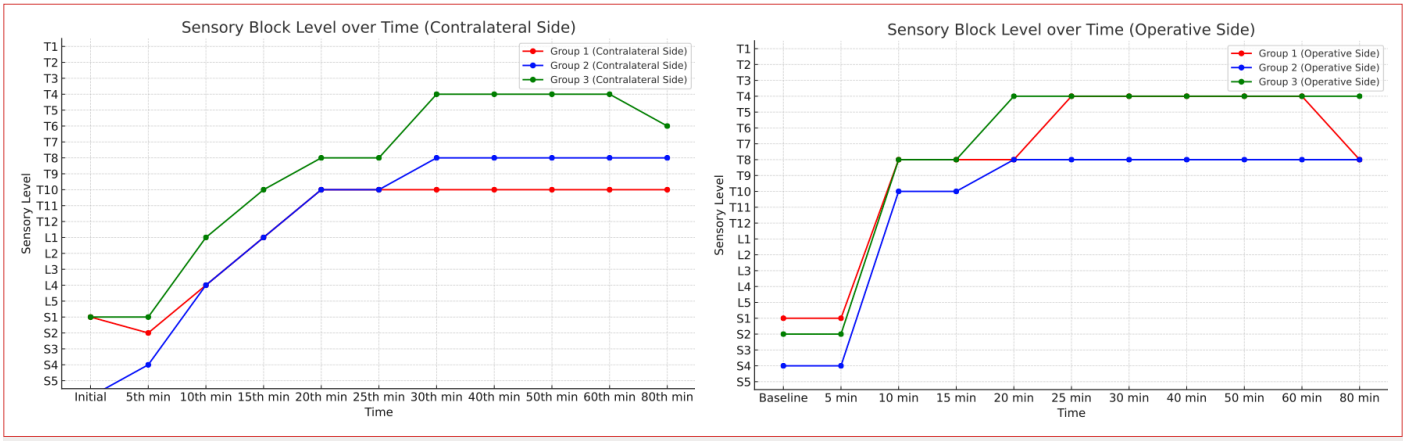

Figure 1. Dermatomal distribution of sensory block levels.

the research, a statistically significant difference was found only in the first 10 min between the operative side and the other side in the intra-group comparisons ($p<0.05$). When comparing the other sides between the groups in the first 10-min segment, lower MBS values were found in Group 1 compared to Groups 2 and 3, and in Group 2 compared to Group 3 (Fig. 2). In Group 1, the sensory and motor blocks of the other side of the patients started significantly later compared to Groups 2 and 3, while the two-segment regressions occurred significantly earlier. The sensory regression times of the other sides of the patients in Group 2 were significantly longer compared to Group 1 and Group 3. It was observed that the significant differences in the sensory block initiation times and two-segment regression times of the patients' operative sides originated from Group 1, whereas the significant difference in sensory regression times originated from Group 2. The operation sides of the patients in Group 1 had significantly earlier sensory block and two-segment regression times compared to Group 2 and Group 3 (Table 3).

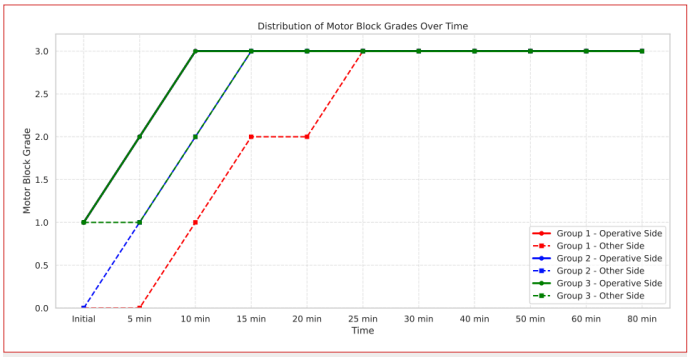

Figure 2. Distribution of engine block grades.

DISCUSSION

This study investigated the effect of spinal column flexion on the quality of unilateral block and hemodynamic safety in patients undergoing inguinal hernia surgery in the lateral decubitus position. The results indicate that spinal anesthesia administered in the flexion position (Group 1) produced a faster and stronger sensory block on the operative side compared to other positions. The contralateral side developed a block later, which enhanced block lateralization. Moreover, Group 1 had lower incidences of hypotension and bradycardia. These results show that the bending position might be able to change how the intrathecal local anesthetics are distributed. Takiguchi et al.[8,9] demonstrated in anatomical studies that flexion of the lower extremities in the lateral decubitus position results in medial displacement of the cauda equina, which may facilitate more targeted intrathecal drug distribution during spinal anesthesia. In this situation, bending the spinal column can be seen as a good way to make isolated blocks.

Spinal anesthesia can induce a sympathetic block, leading to hypotension and bradycardia. By selectively blocking the sympathetic chain on one side, unilateral spinal anesthesia reduces cardiovascular side effects and provides effective surgical anesthesia with a lower dose of local anesthetic. When compared to bilateral spinal anesthesia, the unilateral sympathetic block has a lower chance of low blood pressure because the unblocked side can make up for it. Hence, the risks of low blood pressure, slow HR, sickness, and vomiting that come with high spinal anesthesia can be lowered. Unilateral spinal anesthesia tries to make the anesthesia better and lower the risk of side effects by only blocking movement and sensory nerves in the area that needs it and using less of the anesthetic.[10,11]

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Table 3. Distribution of sensory and motor block onset time, sensory and motor regression time, and two segment recession time for the operative side and the other side within each group and between study groups

	Group 1 (n=20) $\bar{X}$±S (min-max)	Group 2 (n=20) $\bar{X}$±S (min-max)	Group 3 (n=20) $\bar{X}$±S (min-max)	p*
SB Onset time (min)				
Operative Side	1.35±0.49 (1–2)	1.95±0.69 (1–3)	2.20±0.77 (1–3)	0.001[a]
Other Side	7.55±1.64 (5–10)	5.50±1.93 (2–10)	4.65±1.87 (2–8)	<0.001[a]
p-value**	<0.001	<0.001	<0.001	
MB Onset time (min)				
Operative Side	2.25±0.97 (1–5)	2.10±0.64 (1–3)	2.90±1.68 (1-7)	0.247
Other Side	10.50±1.85 (8–15)	7.30±1.87 (5–10)	5.45±2.58 (2–10)	<0.001[a]
p-value**	<0.001	<0.001	<0.001	
Motor regression time (min)				
Operative Side	147.50±28.99 (110–200)	159.00±20.24 (120–180)	163.50±17.55 (130–190)	0.079
Other Side	127.00±30.80 (80–180)	140.50±20.38 (100–180)	148.00±18.24 (120–180)	0.039[b]
p-value**	<0.001	<0.001	<0.001	
Sensory regression time (min)				
Operative Side	191.75±18.52 (150–230)	207.25±17.58 (180–240)	189.50±18.77 (150–210)	0.011[c]
Other Side	169.25±18.94 (140–210)	189.25±18.94 (150–220)	171.00±23.15 (120–200)	0.005[c]
p-value**	<0.001	<0.001	<0.001	
Two-segment regression time (min)				
Operative Side	72.45±6.72 (60–86)	91.10±17.13 (60–150)	84.65±10.34 (60–110)	<0.001[a]
Other Side	67.60±7.50 (50–80)	90.95±15.29 (60–140)	84.65±10.34 (60-110)	<0.001[a]
p-value**	0.001	0.500	1.000	

*Kruskal Wallis Test, **Wilcoxon Signed- Rank Test, a The source of the significent "Group 1," bThe source of the significent between "Group 1" and "Group 3," cThe source of the significent "Group 2." **X**: Mean, S: Standart Deviation, SB: Sensory Block, MB: Motor Block.

According to the research by Esmaoğlu et al.,[12] for unilateral spinal anesthesia, at least 2 mL (10 mg) of hyperbaric bupivacaine should be used for operations above the knee, and 1.5 mL (7.5 mg) should be used for operations below the knee. We decided to use 2.5 mL (12.5 mg) of hyperbaric bupivacaine for spinal anesthesia because our study is in the inguinal area and includes abdominal adjacency. As part of a study, Al Malyan et al.[10] put one group of people under spinal anesthesia while they were lying on their side (lateral decubitus) and another group while they were sitting. Both groups were going to have surgery on their lower abdomens. After the treatment, the patients who had spinal anesthesia were put into the lateral decubitus position while they were still sitting. Both groups stayed in this position for 20 min. In their later follow-ups, they did not find any difference between the groups in terms of the levels of sensory block on the surgical side. However, they did notice that people in the lateral decubitus position got a surgical block much faster than people in the sitting position. These findings highlight the critical role of patient positioning in spinal anesthesia.[11] In our study, the patients were split into three groups. Two groups were put in the lateral decubitus position, which is also known as the fetal position. The third group was put in the lateral decubitus position with the operative side down right after spinal anesthesia was given while they were sitting, and they stayed in this position for 10 min. In Group 1 of these 3, the fetal position that was used during spinal anesthesia was kept up for 10 min without being moved. To make sure the patients in Group 2 and Group 3 had a straight spinal column, they were kept in a lateral decubitus position for 10 min, lying on their side or flat on their back. We then wanted to see what happened to unilateralism when the spinal column bent.

A lot of research was done on the waiting time in unilateral spinal anesthesia. We chose 10 min because we thought that waiting in the lateral decubitus (LD) position for longer would not have a big effect on the unilateral block, taking into account the conditions in the operating room and the flow of the case.

İn our study, there was no significant difference among the groups in the incidence of hypotension or bradycardia. In all

three groups, when patients returned to the supine position after a while, their HR was lower than baseline due to the bilateral spread of the block. For Group 1, these drops in pulse rate were seen after 25 min. For Group 2 and Group 3, they were seen after 10 min. This finding suggests that the decrease in heart rate occurred later in Group 1 compared to Groups 2 and 3. This is because bilateral sympathetic blocking started later in Group 1.

When we looked at other hemodynamic measures in our study, SBP, DBP, and MAP in Group 1 did not change significantly from the starting point. However, in Groups 2 and 3, SBP began to drop sharply after the 3rd min, DBP after the 6th min, and MAP after the 15th min in Group 2 and the 6th min in Group 3. Due to this, hemodynamic changes were not as noticeable in Group 1 where spinal column bending was used. Flexing the spinal column has a good effect on the formation of unilateral blocks, as shown in this case.

To our knowledge, there are not many studies that look at how bending the spinal column affects a single block after spinal anesthesia. Kim et al.[13] did a study where 32 people who were going to have knee arthroscopy were split into two groups. One group (Group F) got spinal anesthesia while lying in a lateral decubitus position and was then kept in this position for 15 min. The other group (Group N) got spinal anesthesia while lying in the same lateral decubitus position and was then kept in this position with their knees stretched out for 15 min. There was not a lot of information in this study about the changes in blood flow between the groups.

When we looked at the patients' sense blocks, we found that in all three groups, the level of blockage on the side that had surgery was higher than the level on the other side. It was seen that in Group 1, the amount of sensory block increased more quickly on the side that had surgery than on the other sides. On the other sides, it increased more slowly. This means that unilateralism worked better in group 1. However, after the 10th min, when the patients were put on their backs, unilateralism got weaker over time, and a block was seen on both sides. Our study, like the one by Kim et al.,[13] found that the group that had spinal column bending had better unilateralism. However, after 15 min, sensory and motor block started to happen on the other side. In Group F, there was no block on the other side for 15 min. In our study, however, after 5 min, a block started to form on the other side.[13] It seems that the reason for this is that the local anesthetics were used at a lower dose and at a slower rate, and the patient waited longer in the LD position, which led to a better unilateral block than ours. In our study, we found that giving local anesthesia for 60 s was the right amount of time. In a study by Enk et al.,[14] it was stressed that a slower application of local anesthetic would give a better unilateral block than a fast infusion.

The type of spinal needle used is another thing that can change how an isolated block forms. One-way needles, especially the Whitacre type needle, have been shown to work better for blocking one side of the body.[15] However, we used the Quincke type spinal needle because our hospital had them.

CONCLUSION

It is known that many factors affect the creation of a unilateral block in the lateral decubitus position. Factors such as the injected dose, baricity, amount of local anesthetic, infusion rate, duration of the lateral decubitus position, and type of spinal needle are known examples of this situation. We believe that spinal column flexion is a good alternative method for creating unilateral blocks, as demonstrated in our study. We believe that due to the limited number of studies conducted on this topic, there is a need for research involving larger series.

DECLARATIONS

Ethics Committee Approval: The study was approved by Kecioren Education and Research Hospital Ethics Committee (No: B.10.4.ISM.4.06.68.49, Date: 22/04/2015).

Informed Consent: Informed consent was obtained from all participants.

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ORIGINAL ARTICLE

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Quantitative Relationship Between Breast Parenchymal Stiffness on Shear-Wave Elastography and Computed Tomography Attenuation: A Single-Center Observational Study

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ABSTRACT

Objective: Breast density reflects fibroglandular tissue composition and affects imaging interpretation and cancer risk. Ultrasound (US) shear-wave elastography (SWE) offers a quantitative method for assessing tissue stiffness. This study aimed to investigate the correlation between breast parenchymal stiffness values measured by SWE and attenuation values obtained from computed tomography (CT).

Materials and Methods: Fifty-four female patients who underwent both breast SWE and chest CT were evaluated. SWE stiffness (kilopascal, kPa) and CT attenuation (Hounsfield Units [HU]) were measured from corresponding parenchymal regions. Correlations were analyzed using Pearson's and Spearman's coefficients, and linear regression analysis was performed.

Results: The mean CT attenuation was −24.8±30.1 HU, and the mean SWE stiffness was 11.7±3.1 kPa. SWE stiffness progressively increased with higher breast parenchymal types according to the Breast Imaging Reporting and Data System classification. CT attenuation and SWE stiffness values demonstrated a strong positive correlation ($r=0.91$, $p<0.001$).

Conclusion: SWE stiffness values strongly correlate with CT attenuation and may serve as a radiation-free surrogate marker for quantitative assessment of breast parenchymal density.

Keywords: Breast density, Breast imaging reporting and data system, Computed tomography, Parenchymal pattern, Shear wave elastography, Stiffness

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INTRODUCTION

Breast tissue composition is highly variable among individuals and is largely determined by the relative proportions of fibroglandular and fatty components. This heterogeneity influences not only breast imaging appearance but also disease risk and diagnostic performance across modalities.[1,2] Breast density, as defined by the Breast Imaging Reporting and Data System (BI-RADS), is an established imaging biomarker associated with both masking effects on mammography and an increased risk of breast cancer.[3,4] Dense parenchyma, which

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contains higher fibroglandular tissue content, exhibits increased attenuation on computed tomography (CT) and greater stiffness on ultrasound (US)-based elastography.[5,6]

Quantitative assessment of tissue stiffness has become feasible with the advent of US shear-wave elastography (SWE), which provides real-time, reproducible measurements of mechanical properties in kilopascals (kPa). SWE has been increasingly applied in breast imaging for lesion characterization, differential diagnosis, and evaluation of parenchymal background.[7-9] Previous studies have demonstrated that SWE values correlate with histologic composition and mammographic density, supporting its role as a surrogate marker of breast microstructure.[10,11]

Although both CT and SWE offer quantitative insights into tissue composition, few studies have directly compared the relationship between CT attenuation (in Hounsfield Units, HU) and SWE stiffness values in normal breast parenchyma. Understanding this relationship may help validate SWE as a radiation-free alternative for quantitative evaluation of breast density and microstructural properties.[12,13]

Therefore, the aim of this study was to investigate the correlation between CT attenuation values and SWE stiffness measurements of the breast parenchyma in female patients, and to assess whether elastography-derived stiffness reflects tissue density as measured by CT.

MATERIALS AND METHODS

Ethics, Study Design, and Population

Ethical approval had been obtained from the institutional review board before data collection, and all procedures were performed in accordance with the Declaration of Helsinki. The study was carried out with the approval and permission of the Academic Board and Ethics Committee of İstanbul Nişantaşı University (date: 14.06.2023, decision No: 2023/24).

The study was conducted at the Radiology Department of BHT Clinic İstanbul Tema Hospital, between July 2023 and October 2025. Among patients referred for breast ultrasonography, those who had undergone chest CT within the previous month for any other clinical indication were selected. During the breast US examination, SWE was additionally performed without imposing any extra physical or financial burden on the patients or the institution. The regions where stiffness measurements were obtained were noted and schematically marked. Subsequently, the patients' chest CT images and US elastography (image and worksheet) findings were evaluated through the imaging archive.

Inclusion criteria were as follows: Patients aged between 20 and 80 years, and cases in which the location of the elastography measurement could be confidently matched with the corresponding region on the chest CT images.

Exclusion criteria were a history of breast surgery, radiation therapy, or any known breast malignancy.

US Features and Examination Protocol

US examinations were performed using a General Electric (GE) LOGIQ S8 (2019) system equipped with a 9 MHz linear transducer and integrated elastography software.

Breast parenchymal patterns were categorized according to sonographic appearance, corresponding to BI-RADS-like density types (A–D), based on the relative proportion of fibroglandular to fatty tissue observed during US evaluation.

SWE measurements were obtained in the upper outer quadrant of the breast, avoiding ducts and focal lesions. For each patient, three valid stiffness measurements (in kPa) were obtained from the same parenchymal area, and the mean value was used for analysis. The acquisition depth ranged between 10 and 30 mm (Fig. 1), and all examinations were performed by a radiologist with 10 years of breast imaging experience.

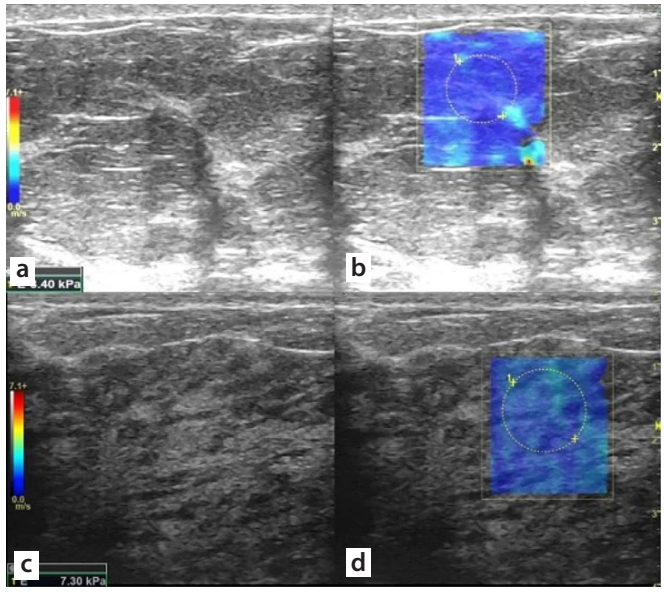

Figure 1. Representative images from two of our cases. The upper images **(a and b)** belong to a 55-year-old female patient and demonstrate the measurement obtained from the fatty parenchymal area. Grayscale ultrasonography image **(a)** and shear-wave elastography (SWE) image **(b)** are shown. In the SWE image **(b)**, the region of interest (ROI) used for stiffness measurement is marked, and the measurement was performed from the upper outer quadrant of the breast. The lower images **(c and d)** belong to a 33-year-old female patient and similarly show the grayscale US image **(c)** and the SWE image **(d)**. In the SWE image **(d)**, the ROI used for stiffness measurement is marked, and the measurement was also performed from the upper outer quadrant of the breast. The quantitative stiffness value in kilopascals (kPa) is displayed in the lower left corner of the images.

CT Acquisition and Attenuation Measurement

All CT examinations were performed on a GE Revolution GSI 256-detector Multislice CT scanner (GE Healthcare, Waukesha, WI, USA). Non-contrast axial images covering the breast parenchyma were analyzed. CT attenuation (HU) measurements for all cases were obtained from the hospital's Digital Imaging and Communications in Medicine Picture Archiving and Communication Systems archive. Using a circular region of interest (ROI) of approximately 1 cm^2 (Fig. 2), attenuation values were recorded in HUs at the corresponding SWE measurement sites, avoiding visible ducts, vessels, or artifacts. Each measurement was repeated three times and averaged for consistency.

Data Analysis and Statistical Methods

US SWE stiffness and CT HU value measurements were obtained from parenchymal regions that corresponded as closely as possible, ensuring maximal anatomical consistency between the two modalities. For each patient, both SWE kPa and CT attenuation values were derived from nearly identical parenchymal sites to achieve optimal comparability across imaging techniques. Both US SWE (kPa) and CT attenuation (HU) measurements were obtained from circular ROIs of approximately 1 cm^2 (100 mm^2).

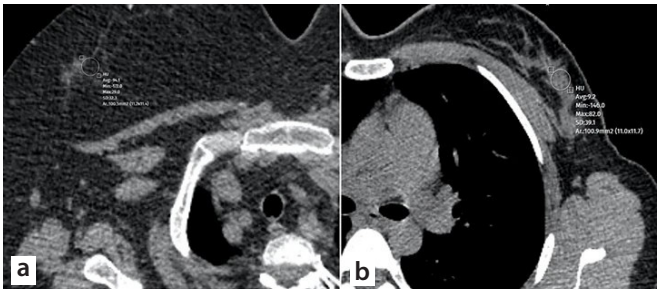

Figure 2. Representative axial chest computed tomography (CT) images demonstrating CT attenuation (hounsfield unit) measurements. These images show the location and technique of attenuation measurement corresponding to the regions where ultrasonographic imaging and stiffness assessment were performed in the same patients. The measurements were obtained from the parenchymal areas within the regions of interest, indicated by thin white circles. The image on the left **(a)** belongs to a 57-year-old female patient, with the measurement obtained from the upper outer quadrant of the right breast, while the image on the right **(b)** belongs to a 42-year-old female patient, with the measurement obtained from the upper outer quadrant of the left breast.

Statistical analyses were performed using the Statistical Package for the Social Sciences version 26.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were expressed as mean±standard deviation, and categorical variables as numbers and percentages. Normality was evaluated using the Shapiro–Wilk test. The correlation between CT attenuation (HU) and SWE stiffness (kPa) was assessed using both Pearson's and Spearman's correlation coefficients. A simple linear regression model was used to determine the relationship between HU and SWE values. Statistical significance was set at $p<0.05$.

RESULTS

A total of 54 female patients with a mean age of 42.4±11.0 years (range, 20–78 years) were included in the analysis. Of these, 36 (66.7%) were premenopausal and 18 (33.3%) were postmenopausal. According to the BI-RADS breast density classification, 10 patients (18.5%) were type A, 19 (35.2%) type B, 16 (29.6%) type C, and 9 (16.7%) type D (Table 1).

The mean CT attenuation value of breast parenchyma was −24.8±30.1 HU, whereas the mean SWE stiffness was 11.7±3.1 kPa. SWE stiffness values gradually increased with higher BI-RADS density categories. The mean stiffness values were 7.5±1.6 kPa in type A, 10.4±1.8 kPa in type B, 13.2±2.0 kPa in type C, and 15.6±2.1 kPa in type D parenchyma, demonstrating a stepwise pattern of increasing tissue stiffness with increasing CT attenuation ($p<0.001$) (Table 1).

A strong, positive correlation was observed between CT attenuation and SWE stiffness (Pearson $r=0.91$, Spearman $\rho=0.92$, both $p<0.001$) (Table 2 and Fig. 3). The linear regression model showed that CT density significantly predicted SWE stiffness ($\beta=0.10\pm0.01$, 95% CI=0.08–0.12, $p<0.001$). The regression equation was defined as:

$$SWE\ (kPa)=4.0+0.10\times(CT\ HU+100)$$

Indicating that for every 10 HU increase in CT density, the SWE stiffness increased by approximately 1 kPa.

DISCUSSION

In this study, a significant positive correlation was observed between breast parenchymal stiffness values measured by SWE and attenuation values obtained from CT. These findings suggest that SWE-derived stiffness is closely related to tissue composition and density, as represented by HU values on CT. Similar relationships between SWE stiffness and parenchymal density have been reported in previous studies evaluating quantitative elastography in breast tissue.[14,15]

Previous investigations demonstrated that dense breast tissue, containing a higher proportion of fibroglandular elements, exhibits both higher stiffness values on elastography and higher attenuation on CT compared with fatty tissue.[6,16]

Table 1. Demographic and imaging characteristics of the study population (n=54)

Variable	Category / Range	n (%) or Mean±SD
Age (years)	20–78	42.4±11.0
Menopausal status		
Premenopausal	36 (66.7%)	
Postmenopausal	18 (33.3%)	
BI-RADS category		
A (Homogeneously hypoechoic parenchyma with predominantly fatty tissue)	10 (18.5%)	
B (Hypoechoic background with scattered linear or patchy hyperechoic fibroglandular areas)	19 (35.2%)	
C (Irregular or heterogeneous echotexture with multiple hyperechoic fibroglandular areas)	16 (29.6%)	
D (Diffusely hyperechoic parenchyma with minimal fatty areas)	9 (16.7%)	
CT attenuation (HU)	−100 to +45	−24.8±30.1
SWE stiffness (kPa)	3.8–17.9	11.7±3.1
Side of measurement	Right / Left	25 (46.3%) / 29 (53.7%)
Depth of measurement (mm)	10–30	19.8±4.7

BI-RADS: Breast Imaging Reporting and Data System; CT: Computed Tomography; HU: Hounsfield Unit; kPa: kilopascal; mm: millimeter; SD: Standard deviation; SWE: Shear-Wave Elastography.

Table 2. Correlation and linear regression analysis between CT HU and SWE kPa

Variable	Pearson r	Spearman ρ	p	Linear regression (β±SE)	95% CI for β	p
CT attenuation (HU)	0.91	0.92	<0.001	0.10±0.01	0.08 – 0.12	<0.001

β: Standardized regression coefficient; CI: Confidence interval; HU: Hounsfield Unit; kPa: kilopascal; p: Probability value; r: Pearson correlation coefficient; ρ: Spearman rank correlation coefficient; SE: Standard error; SWE: Shear-Wave Elastography.

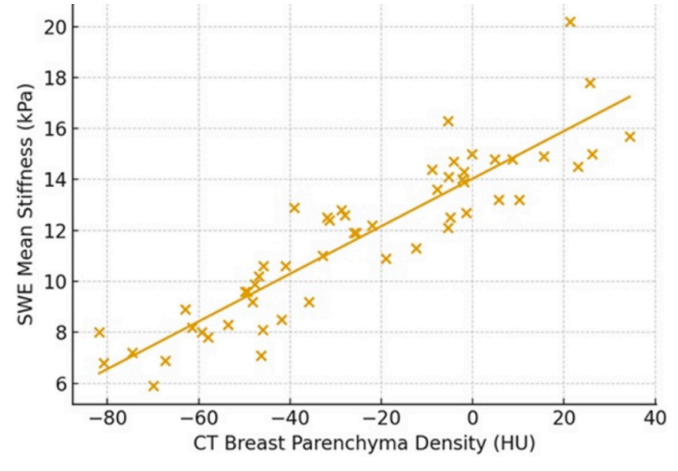

Figure 3. Correlation between computed tomography hounsfield unit and shear-wave elastography stiffness (kPa) in breast parenchyma. Scatter plot illustrating the positive relationship between the two parameters.

Our results are consistent with those reports, demonstrating a stepwise increase in stiffness across BI-RADS density categories, from type A (predominantly fatty) to type D (extremely dense) parenchyma. This relationship supports the physiologic link between tissue microstructure and its mechanical and radiological properties.[5]

Several authors have highlighted the diagnostic value and reproducibility of SWE in breast imaging.[8,9] The strong correlation (r=0.91) observed in our study suggests that SWE stiffness can serve as a reliable quantitative biomarker reflecting breast density and fibroglandular composition. Because both HU and SWE respond to tissue composition, SWE may provide a non-ionizing, reproducible alternative for estimating parenchymal density in women who require frequent imaging follow-up.[10]

The potential integration of SWE into breast density assessment is also noteworthy. Mammographic density has been recognized as an independent risk factor for breast cancer, and SWE could complement mammographic evaluation by providing addition-

al biomechanical information.[4,17] Combining SWE findings with CT or magnetic resonance imaging-based metrics could enhance personalized risk stratification and screening protocols.[18]

The limitations of this study include its modest sample size and single-center setting. Another limitation is that, since the measurements were obtained using different imaging modalities, an exact millimeter-to-millimeter overlap of the measurement locations could not be achieved. Furthermore, although the time interval between CT and US examinations did not exceed one month, variations in breast parenchymal composition – particularly in women of reproductive age – may have influenced the results. In addition, stiffness and attenuation values may vary depending on differences in imaging systems or acquisition parameters. Nevertheless, the strong correlation observed between the measurements supports the reliability of the findings. Future multicenter studies incorporating histopathological correlation are warranted to validate these results and to further clarify their clinical implications.[19,20]

CONCLUSION

This study demonstrated a strong, positive correlation between breast parenchymal stiffness measured by SWE and attenuation values obtained from CT. The results indicate that elastography-derived stiffness reliably reflects tissue density and composition, supporting its potential role as a radiation-free surrogate for quantitative assessment of breast parenchymal characteristics. Integration of SWE into breast imaging protocols may improve evaluation of parenchymal density and contribute to more personalized diagnostic and screening strategies. Further prospective, large-scale studies are warranted to validate these findings and explore their clinical implications.

DECLARATIONS

Ethics Committee Approval: The study was approved by İstanbul Nişantaşı University Ethics Committee (No: 2023/24 Date: 14/06/2023).

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

Conflict of Interest: The authors declare that there is no conflict of interest.

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Peer-review: Externally peer-reviewed.

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Changes in HALP Score After Interventional Therapy in Treatment-Resistant Chronic Migraine: A Retrospective Cohort of Responders

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ABSTRACT

Objective: Chronic migraine (CM) is a disabling neurovascular disorder often linked to systemic low-grade inflammation. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score has been proposed as an integrative biomarker of nutritional and inflammatory status; however, its role in migraine remains unclear. This study examined whether HALP improves after interventional therapy in treatment-resistant CM and whether changes correlate with clinical outcomes.

Materials and Methods: This retrospective study included 128 CM patients who were unresponsive to ≥3 months of pharmacological prophylaxis and subsequently achieved a ≥50% reduction in monthly headache frequency after interventional treatment were analyzed. Patients received either repetitive greater occipital nerve blocks or pulsed radiofrequency. Clinical outcomes (headache frequency, numerical rating scale (NRS), and analgesic consumption) and laboratory parameters (hemoglobin, albumin, lymphocyte, and platelet counts) were recorded at baseline and 6 months. HALP was calculated as (Hemoglobin (g/L) × Albumin (g/L) × Lymphocyte count ($\times 10^9$/L) / Platelet count ($\times 10^9$/L)). Associations were tested with Spearman's ρ.

Results: At 6 months, patients showed significant improvements: NRS decreased from 8.0 (7.0–9.0) to 3.0 (3.0–4.0), headache frequency from 19.0 (16.8–21.0) to 3.0 (2.0–4.0), and analgesic consumption from 8.0 (6.0–9.0) to 3.0 (2.0–4.0) tablets/month (all $p<0.001$). HALP increased from 49.3 (36.2–58.4) to 66.5 (56.0–75.7) ($p<0.001$). ΔHALP was weakly but statistically significantly correlated with reduced headache frequency ($\rho=0.195$, $p=0.027$), but not with ΔNRS ($\rho=0.091$, $p=0.308$) or Δanalgesic consumption ($\rho=0.103$, $p=0.246$).

Conclusion: Interventional treatments for CM were associated with significant increases in HALP scores, suggesting modulation of systemic inflammatory–nutritional status. As ΔHALP was only weakly related to reduced attack frequency and unrelated to pain intensity or analgesic use, HALP may reflect biological changes at the group level and could serve as a monitoring biomarker; however, its individual-level clinical relevance appears to be limited.

Keywords: Albumin, Chronic migraine, Hemoglobin, lymphocyte, Nerve block, Neuroinflammation, platelet score, Pulsed radiofrequency, Systemic biomarker

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INTRODUCTION

Chronic migraine (CM) is a disabling neurological disorder characterized by frequent headache episodes that significantly impair quality of life and daily functioning. It is estimated that approximately 1–2% of the global population is affected by CM, with a higher prevalence among women and individuals of working age.[1] According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), CM is defined as headache occurring on 15 or more days per month for more than 3 months, with features of migraine headache on at least 8 of those days.[2] Compared to episodic migraine, CM is associated with greater disease burden, including increased attack frequency, higher rates of medication overuse, psychiatric comorbidities, and a lower health-related quality of life.[3]

For patients with CM who do not respond to medical treatment, greater occipital nerve (GON) block and pulsed radiofrequency (PRF) therapy are two effective interventional methods. A GON block reduces neuronal stimulation by targeting the peripheral nerves, while PRF therapy provides long-term pain relief by modulating the nerve at low temperatures. Both methods have been reported to effectively reduce the frequency and intensity of pain.[4-7]

The pathophysiology of CM is complex and multifactorial, involving central sensitization, altered pain modulation, and potentially, sustained neuroinflammatory processes.[8]

Although the exact mechanisms are not fully understood, a body of evidence suggests that neurogenic inflammation and systemic immune dysregulation play a significant role in the development of migraines.[9,10]

Neuroinflammatory cascades involve the activation of the trigeminovascular system, the release of vasoactive neuropeptides such as calcitonin gene-related peptide, and the upregulation of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6.[11-13] These mediators promote the persistence and chronicity of migraine attacks by increasing the excitability of both peripheral and central nociceptors.[14] Alongside these mechanisms, several hematologic markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and C-reactive protein (CRP), have been investigated as peripheral indicators of systemic inflammation in migraine patients.[15-17] More recently, broader inflammatory indices have also been proposed, including systemic immune–inflammation-based scores[18] and composite biomarker approaches,[19] highlighting the increasing recognition of migraine as a disorder with systemic inflammatory underpinnings. However, these parameters only reflect individual components of the inflammatory response and may not fully capture the complexity of immune-nutritional interactions in chronic pain conditions.

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a composite biomarker initially developed in oncology to reflect the combined state of hematological, nutritional, and inflammatory pathways.[20] In contrast to unidimensional biomarkers, the HALP score integrates multiple physiological components: hemoglobin, reflecting oxygen transport capacity and anemia; albumin, representing nutritional status and hepatic synthetic function; lymphocytes, as markers of immune competence; and platelets, which participate in proinflammatory processes. Each of these parameters is known to be modulated by systemic inflammation, physiological stress, and chronic pain factors intrinsically linked to the pathophysiology of migraine.[14] Despite its theoretical relevance, the HALP score has not yet been explored in patients with migraine. In this study, we aimed to evaluate the changes in HALP scores from pre- to post-treatment among patients with CM who underwent a standardized interventional protocol involving either a GON block or PRF therapy. We hypothesized that a significant reduction in headache frequency would be associated with an improvement in HALP scores. Furthermore, we aimed to investigate whether HALP may serve as a novel integrative biomarker of systemic inflammation in the management of migraine. If validated, the HALP score could serve as a simple and cost-effective tool to monitor treatment response or stratify inflammatory burden in clinical practice.

MATERIALS AND METHODS

Ethical Considerations

The study was approved by the Local Ethics Committee (Approval No: 12/14; Date: July 17, 2025). This retrospective analysis of anonymized patient data was conducted in accordance with the principles of the Declaration of Helsinki. The committee waived the requirement for informed consent, as permitted by institutional and national regulations.

Study Design and Population

This retrospective observational study was conducted at the pain clinic of a tertiary education and research hospital between January 2023 and June 2025. Adult patients diagnosed with CM based on the ICHD-3 criteria, who had undergone at least 3 months of standard pharmacological prophylaxis without meaningful clinical response, were included. They were referred to our clinic for interventional treatment due to frequent and severe migraine attacks.

Only patients demonstrating a ≥50% reduction in monthly headache frequency at 6 months post-treatment were

included in the final analysis. Although a controlled group was initially considered, the small number of non-responders (*n*=7) precluded meaningful statistical comparison. Therefore, pre-treatment clinical status served as the internal control for within-subject comparisons.

Inclusion Criteria

Patients aged 18–65 years, diagnosed with CM per ICHD-3, receiving standard prophylactic therapy for at least 3 months without adequate control of attacks, with available pre- and post-treatment laboratory data (CBC and albumin), and who underwent standardized interventional treatment.

Exclusion Criteria

Medication overuse headache, acute or chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease, and vasculitis), autoimmune diseases, hematological disorders or malignancies, active infection or fever within 14 days before evaluation, chronic liver or renal failure, cachexia, corticosteroid or immunosuppressive use, pregnancy or breastfeeding, and incomplete medical records.

Treatment Protocol

Experienced pain physicians performed all procedures under sterile conditions.

GON Block

A 25-gauge needle was introduced at the level of the occipital protuberance using anatomical landmarks. After negative aspiration, 2 mL of a mixture containing 1 mL 0.5% bupivacaine and 1 mL 2% lidocaine was injected per side. No corticosteroids were used. Blocks were performed weekly for the first 4 weeks, and then every other week for a total of 8 sessions.

PRF of the GON

Following local anesthesia, a 22-gauge, 5-mm active tip radiofrequency cannula was advanced toward the GON guided by anatomical landmarks. Correct positioning was confirmed through sensory stimulation at 50 Hz (paresthesia at ≤0.5 V) and the absence of a motor response at 2 Hz. PRF was applied at 65 V, 42°C, 20 ms pulse width, 2 Hz frequency, for 240 s (2 cycles×120 s). The maximum tip temperature did not exceed 42°C.

Minor complications (bleeding, dizziness, local pain) were recorded immediately after the procedure and during follow-up; no serious adverse events occurred.

Data Collection

Data integrity was ensured through comprehensive clinical documentation. A successful treatment response was defined as a ≥50% reduction in monthly headache frequency, consistent with the International Headache Society and American Headache Society guidelines. Initially, medical records of patients diagnosed with CM who underwent either GON block or PRF between June 2023 and June 2025 were reviewed, identifying a total of 189 cases. Fifty-four patients were excluded due to missing baseline data (*n*=13), loss to follow-up (*n*=17), or unavailable laboratory values at the 6-month visit (*n*=24). Due to the limited number of non-responders (*n*=7), only responders were included in the final analysis. Ultimately, 128 responders were included in the final analysis (Fig. 1).

Extracted data comprised demographic variables (age, sex); clinical characteristics (disease duration in months, pain intensity using the numerical rating scale (NRS, 0–10), monthly headache frequency, and analgesic consumption); and laboratory parameters (hemoglobin, lymphocyte count, platelet count, and serum albumin), recorded at baseline and

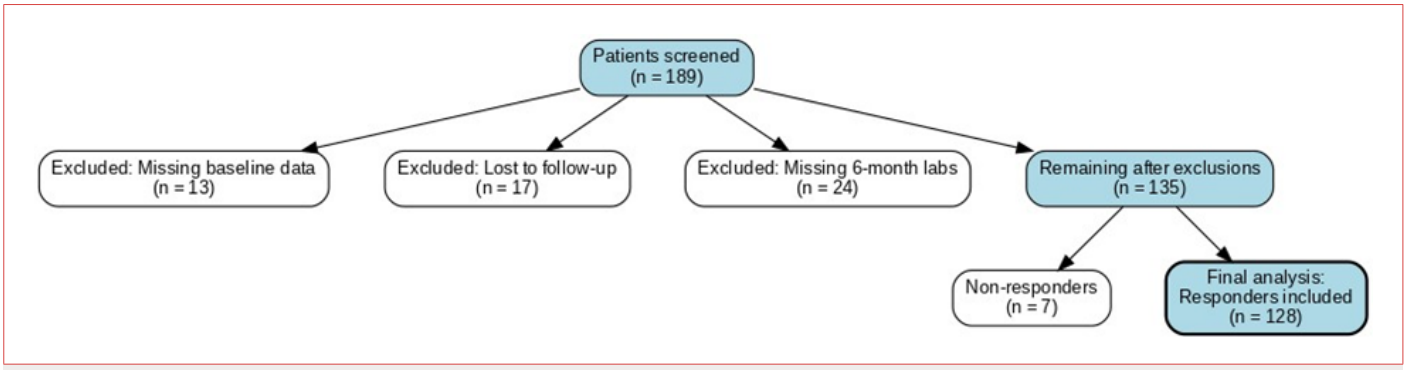

Figure 1. Flowchart of patient selection and inclusion process. A total of 189 patients with chronic migraine were initially screened. After exclusions for missing baseline data (*n*=13), loss to follow-up (*n*=17), and absence of 6-month laboratory values (*n*=24), 135 patients remained. Of these, 7 did not achieve the predefined treatment response and were excluded. The final analysis included 128 responders.

at the 6-month follow-up. To minimize bias, data extraction and screening were conducted by a researcher independent of the treating physician.

The primary outcome was the change in the HALP score, calculated as:

HALP=Hemoglobin (g/L)×Albumin (g/L)×Lymphocyte count ($\times 10^9$/L)/Platelet count ($\times 10^9$/L).

This composite index reflects systemic inflammatory and nutritional status; an increase is considered indicative of systemic improvement. Secondary analyses examined the correlation between HALP changes and clinical outcomes, including pain intensity (as measured by the NRS), attack frequency, and analgesic consumption.

Laboratory analyses were performed using standardized automated analyzers at the institutional central biochemistry and hematology laboratories, with both internal quality control and external accreditation procedures. Reference ranges were: hemoglobin 135–180 g/L (males) and 125–160 g/L (females); serum albumin 35–52 g/L; lymphocyte count 1.16–3.18 $\times 10^9$/L; and platelet count 150–450 $\times 10^9$/L.

Statistical Analysis

All statistical analyses were planned a priori, with distributional assumptions checked before inferential testing. Continuous variables were summarized as median (interquartile range, IQR), and categorical variables as *n* (%). Normality was assessed using the Shapiro–Wilk test and by visual inspection of distributions. Given that key outcomes (monthly attack frequency, NRS, and analgesic consumption) exhibited non-normal distributions and several laboratory variables did not consistently meet normality across subgroups, non-parametric methods were adopted for inference.

Within-subject changes from baseline to 6 months were tested using the Wilcoxon signed-rank test. Between-group comparisons (repetitive GON blocks vs. PRF, PRF) used the Mann–Whitney U-test for continuous variables and Pearson's χ^2 (or Fisher's exact when appropriate) for categorical variables.

Change scores (Δ) were coded so that higher values reflect clinical improvement: ΔNRS = baseline − month 6; Δanalgesic consumption = baseline − month 6; Δattack frequency = baseline − month 6; and ΔHALP = month 6 − baseline.

Associations between changes in HALP (ΔHALP) and clinical outcomes were examined with Spearman's rank correlation (ρ). For all primary analyses, effect sizes were reported ($r=z/\sqrt{N}$ for Wilcoxon) together with 95% confidence intervals for median differences (bootstrap, B=10,000) and for correlation coefficients (Fisher's z approximation). All p-values were two-sided with α=0.05; very small p-values are reported as p<0.001. All analyses were performed using IBM Statistical Package for the Social Sciences Statistics, version 25.

RESULTS

A total of 128 patients were included (110 females [85.9%], 18 males [14.1%]) with a mean age of 44.4±10.7 years and a mean disease duration of 8.1±2.6 months. Based on the interventional approach, 88 patients (68.8%) underwent repeated GON blocks, while 40 patients (31.2%) received PRF. Baseline distributions were comparable between groups, with no significant differences in age, sex, disease duration, baseline headache frequency, NRS, analgesic consumption, or HALP (all p>0.05).

At 6 months, patients demonstrated significant improvements in all clinical outcomes. Median NRS decreased from 8.0 (7.0–9.0) to 3.0 (3.0–4.0), with a median reduction of 5.0 (95% CI, 4.0–6.0; Wilcoxon r=0.82; p<0.001). Analgesic consumption declined from 8.0 (6.0–9.0) to 3.0 (2.0–4.0) tablets/month, corresponding to a median reduction of 5.0 (95% CI, 4.0–6.0; r=0.78; p<0.001). Monthly headache frequency decreased from 19.0 (16.8–21.0) to 3.0 (2.0–4.0), with a median reduction of 16.0 (95% CI, 15.0–17.0; r=0.89; p<0.001). Laboratory measures also improved, including increases in hemoglobin, albumin, and lymphocyte counts, decreases in platelet counts, and a marked rise in HALP (49.3 [36.2–58.4] to 66.5 [56.0–75.7]; median difference 16.0 [12.0–20.0]; r=0.71; p<0.001, Table 1).

Correlation analyses showed that ΔHALP was weakly but significantly associated with reductions in monthly headache frequency (ρ=0.195; 95% CI, 0.020–0.361; p=0.027), whereas correlations with ΔNRS (ρ=0.091; 95% CI, −0.084–0.261; p=0.308) and Δanalgesic consumption (ρ=0.103; 95% CI, −0.072–0.272; p=0.246) were not significant (ρ=0.195, p=0.027; Table 2 and Fig. 2).

Subgroup Analysis

Age distributions did not differ significantly between the block and PRF groups (Mann–Whitney U, p=0.140), and female predominance was similar (85.2% vs. 87.5%; χ^2, p=0.95).

Both treatment groups showed significant reductions in monthly migraine frequency at 6 months (Wilcoxon, both "p<0.001). In the block group, frequency decreased from 19.0 ([17.0–21.0] to 3.0 [2.0–4.0]; in the PRF group, from 19.0 [17.0–22.0] to 3.0 [2.0–4.0] (baseline in Table 1; 6-month distributions in Table 3).

Between-group comparisons showed no significant differences at baseline (age p=0.140; disease duration p=0.874; attack

Table 1. Change from Baseline to 6 Months (Wilcoxon, Effect Size, CI).

Variable	Baseline median (IQR)	6 mo median (IQR)	Median difference (6mo – Baseline)	Wilcoxon p	Effect size r	N
NRS	8.0 (7.0–9.0)	3.0 (3.0–4.0)	−5.0 (−6.0 to −4.0)	<0.001	−0.862	128
Analgesic consumption (tabs/mo)	8.0 (6.0–9.0)	3.0 (2.0–4.0)	−5.0 (−6.0 to −4.0)	<0.001	−0.853	128
Attack frequency (/mo)	19.0 (16.8–21.0)	3.0 (2.0–4.0)	−16.0 (−17.0 to −15.0)	<0.001	−0.869	128
Hemoglobin (g/L)	124.5 (121.0–132.0)	129.0 (124.0–135.0)	+4.0 (+3.0 to +5.0)	<0.001	+0.737	128
Albumin (g/L)	41.3 (39.8–44.3)	43.4 (41.4–46.7)	+2.1 (+1.4 to +2.5)	<0.001	+0.744	128
Lymphocyte ($\times10^9$/L)	2.1 (1.8–2.3)	2.3 (2.1–2.6)	+0.2 (+0.1 to +0.2)	<0.001	+0.408	128
Platelet ($\times10^9$/L)	228.5 (196.0–291.5)	198.0 (176.0–222.0)	−30.0 (−31.0 to −19.0)	<0.001	−0.725	128
HALP	49.3 (36.2–58.4)	67.1 (56.0–75.7)	+17.0 (+15.0 to +20.0)	<0.001	+0.830	128

Median difference was calculated as (6 months − Baseline). Accordingly, positive values denote an increase and negative values denote a decrease. Effect size r (Wilcoxon) is reported with its sign to indicate the direction of change. NRS: Numerical Rating Scale; mo: month; tabs: tablets; g/L: grams per liter; $\times10^9$/L: cells $\times10^9$ per liter; HALP: Hemoglobin×Albumin×Lymphocyte/Platelet.

Table 2. Correlations between ΔHALP and clinical improvements at 6 months.

Outcome (Δ, + = improvement)	Spearman ρ	95% CI	p-value	N
NRS (baseline – 6 months)	0.091	(-0.084, 0.261)	0.308	128
Analgesic consumption (baseline – 6 months)	0.103	(-0.072, 0.272)	0.246	128
Attack frequency (baseline – 6 months)	0.195	(0.020, 0.361)	0.027*	128

Notes: Δ values coded so that positive numbers reflect clinical improvement (e.g., ΔNRS=baseline – 6 months; ΔHALP=6 months – baseline). 95% CI: confidence interval. *p<0.05.

frequency p=0.690; NRS p=0.359; analgesic consumption p=0.681; HALP p=0.748; Table 1) or at 6 months (attack frequency p=0.504; NRS p=0.222; analgesic consumption p=0.484; HALP p=0.464; Table 3).

In subgroup analyses, HALP scores increased from baseline to 6 months in both groups. In the PRF group, ΔHALP was not significantly correlated with changes in headache frequency (ρ=0.16, p=0.31), NRS (ρ=−0.14, p=0.39), or analgesic consumption (ρ=0.13, p=0.44). In the block group, a weak but statistically significant positive correlation was observed between ΔHALP and reduction in monthly headache frequency (ρ=0.22, p=0.038). In contrast, correlations with ΔNRS (ρ=0.20, p=0.066) and Δanalgesic consumption (ρ=0.07, p=0.54) were not significant (Table 4).

Table 3. Six-month outcomes by treatment group (Block vs PRF).

Variable	Block	PRF	p-value
NRS at 6 Months	3.00 (3.00–4.00)	3.00 (2.75–4.00)	0.222
Analgesic consumption at 6 Months (tablets/mo)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	0.484
Attack Frequency at 6 Months (episodes/mo)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	0.504
Hemoglobin 6 Months (g/L)	130.00 (124.00–134.25)	129.00 (124.75–135.00)	0.971
Albumin 6 Months (g/L)	43.55 (41.38–46.40)	43.25 (41.38–47.62)	0.992
Lymphocyte 6 Months ($\times10^9$/L)	2.32 (2.08–2.59)	2.31 (2.06–2.54)	0.616
Platelet 6 Months ($\times10^9$/L)	198.00 (176.00–217.25)	204.50 (177.50–250.75)	0.275
HALP 6 Months	67.52 (58.41–75.57)	64.55 (50.35–76.02)	0.464

Notes: Six-month clinical and laboratory outcomes are summarised as median (IQR). Between-group comparisons used the Mann–Whitney U test (two-sided, α=0.05). PRF, pulsed radiofrequency; IQR: Interquartile range; NRS: Numerical rating scale; HALP, hemoglobin×albumin×lymphocyte/platelet.

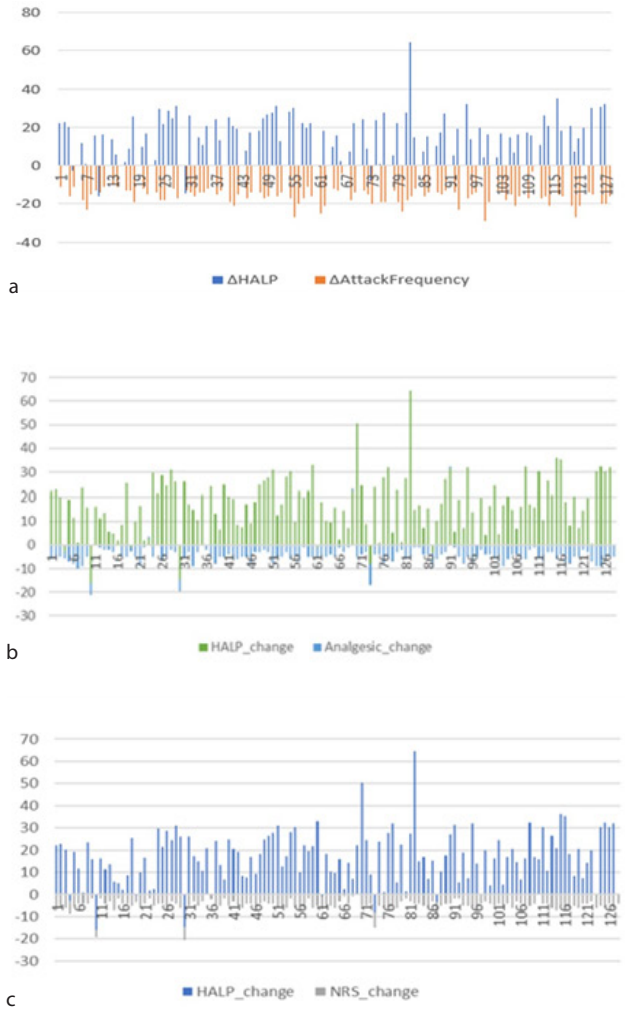

Figure 2. Associations between Δ hemoglobin, albumin, lymphocyte, and platelet (HALP) and clinical parameters at 6 months: Attack frequency, pain intensity (numerical rating scale [NRS]), and analgesic consumption. **(a)** ΔHALP versus reduction in monthly headache frequency. **(b)** ΔHALP versus reduction in analgesic consumption. **(c)** ΔHALP versus reduction in NRS.

DISCUSSION

In our study, patients who underwent either repetitive GON blocks or PRF treatment showed a significant increase in HALP scores after treatment (from 48.78±14.39 to 65.37±14.29, p<0.001). To the best of our knowledge, this is the first study to longitudinally evaluate the HALP score in treatment-resistant CM following GON blocks or PRF, and to relate the change in HALP score (ΔHALP) to clinical outcomes. This improvement may reflect not only clinical recovery but also a modulation of systemic inflammatory and nutritional status. However, since only responders were included in the analysis, the limited variability should be considered when interpreting biomarker–outcome associations. The increase in HALP showed a statistically significant but weak association with reductions in monthly attack frequency, indicating a limited link between systemic biological changes and clinical response. Given the responder-only design and the limited variability, HALP should be viewed as a biological trend at the group level for now. It does not seem to be a reliable predictor for individual patients.

Table 4. Subgroup correlations of ΔHALP with clinical improvement (Block and PRF analysed separately).

Clinical Parameter	Spearman's ρ	p-value
PRF Group		
Change in headache frequency	0.1632	0.314
Change in NRS	-0.1403	0.388
Change in analgesic consumption	0.1267	0.436
Block Group		
Change in headache frequency	0.2219	0.038
Change in NRS	0.1972	0.066
Change in analgesic consumption	0.0662	0.540

Notes: Within-group associations between ΔHALP and changes in monthly headache frequency, NRS, and monthly analgesic consumption were assessed using Spearman's rank correlation (ρ) (two-sided, α=0.05). Results are presented separately for the Block and PRF subgroups. Abbreviations: PRF, pulsed radiofrequency; NRS: Numerical Rating Scale; Δ, change from baseline to 6 months.

No significant correlations were found with pain intensity (NRS) or analgesic consumption. This dissociation aligns with prior observations that systemic inflammatory indices correlate more closely with disease activity than with subjective pain perception.

NLR, CRP, and cytokine levels, which are often correlated with migraine burden but not consistently with pain intensity.[9,15,21] Accordingly, HALP is best positioned as a monitoring biomarker of biological disease activity rather than a surrogate for pain severity. While the subgroup signal looked more evident in the nerve block cohort, single-session PRF is generally considered clinically comparable to repeated blocks, and our analysis was not powered to test between-modality differences. Therefore, we think this difference is preliminary and likely due to the small sample size, rather than a real biological difference between the treatments.

In recent years, the HALP score has emerged as a comprehensive biomarker of systemic inflammatory and nutritional status,

particularly in oncology. Studies have demonstrated that low HALP values are associated with a poor prognosis. At the same time, higher scores are linked to better survival and improved treatment responses in cancers such as stomach, colon, lung, and bladder.[20,22] Moreover, large-scale cohort studies have suggested a non-linear association between HALP and mortality.[23] Beyond oncology, the HALP score has also been evaluated as a systemic predictor of outcomes in ischemic stroke, cardiovascular disease, and diabetic complications.[24,25] Low HALP scores have been associated with a poor prognosis in several neuroinflammatory and metabolic disorders.[26] Beyond oncology, the role of HALP in chronic pain and migraine is largely unexplored. Given reports of non-linear (e.g., thresholded or J-shaped) associations in other populations,[23] future studies should explicitly test for non-linearity (e.g., using restricted cubic splines) rather than assume linear effects.

At a component level, the overall HALP rise in our cohort appears to be driven primarily by platelet deactivation and lymphocyte recovery, with albumin and hemoglobin contributing more modestly—an immune-hematologic pattern compatible with attenuation of attack-related neuroinflammation and platelet hyperactivation. These patterns align with reports of platelet hyperactivation and immune dysregulation during migraine attacks.[27-31] Among the HALP components, albumin is a negative acute-phase reactant that tends to increase with suppression of inflammation.[32] In our cohort, the rise in albumin was a key factor driving HALP improvement, which may reflect a reduced inflammatory burden. Control of migraine attacks may have led to lower cytokine levels (e.g., IL-6, TNF-α), which normally inhibit hepatic albumin synthesis, alongside improvements in nutritional status and oral intake. The increase in hemoglobin levels is also noteworthy. Hemoglobin reflects both erythropoiesis and systemic health; iron deficiency anemia is frequently reported in migraine patients and may be associated with an increased frequency of attacks.[33,34] Thus, the post-treatment increase in hemoglobin may represent systemic recovery, although its direct effect on migraine outcomes remains uncertain.

The observed rise in lymphocyte counts supports the concept that migraine is not solely a vascular disease but also involves immune-mediated neuroinflammation. Elevated NLR during acute migraine, driven by neutrophilia and lymphocytopenia, is considered an inflammatory marker.[27] Therefore, an increase in lymphocyte levels following treatment could indicate regression of systemic inflammation and rebalancing of immune function. In parallel, the reduction in platelet counts after treatment is consistent with reports of platelet hyperactivation during migraine attacks.[28-31] This hematologic response may reflect control of systemic inflammation and contribute to the overall HALP increase. Standardizing preanalytical conditions for blood sampling (fasting status, time of day, and interictal timing) would further reduce biological and circadian variability in HALP and its components. Standardization would also facilitate between-study comparability and reduce preanalytical bias in composite scores such as HALP.

This study has several limitations. First, the retrospective and non-randomized design without a control group precludes causal inference. Importantly, patients served as their own internal controls through within-subject pre–post comparisons, which partially mitigates the absence of an external control group. Although a comparative group of non-responders was initially considered, the minimal number of such cases (n=7) prevented meaningful analysis. All interventions were performed by a single-experienced pain specialist using standardized protocols, while data collection was conducted independently by a blinded investigator, reducing bias. Nevertheless, unmeasured confounders such as nutritional intake, albumin kinetics, iron repletion, body weight change, intercurrent infection or inflammation, menstrual phase, hydration, and adjustments in preventive pharmacotherapy may have influenced HALP independently of the procedures. Given multiple endpoints and subgroup analyses, correlation findings should be regarded as exploratory; confirmatory work should prespecify outcomes and control for multiplicity. Finally, the responder-only frame restricts variability and likely attenuates biomarker–outcome coupling; inclusion of non-responders in prospective cohorts is essential.

CONCLUSION

The significant increase in HALP scores observed after interventional therapy may represent a systemic biological response in CM. Given the chronic low-grade neuroinflammation underlying migraine, HALP may provide indirect insights into inflammatory activity and treatment response in this population. While HALP has been widely studied in oncology and cardiometabolic conditions, to our knowledge, this is the first report on its potential relevance in treatment-resistant CM. Overall, HALP currently appears to be more suited for monitoring biological activity than for predicting individual clinical responses. These results are hypothesis-generating, and further prospective, randomized, large-scale studies are warranted to validate HALP as a monitoring biomarker in migraine management.

DECLARATIONS

Ethics Committee Approval: The study was approved by Antalya Training and Research Hospital Ethics Committee (No: 12/14 Date: 17/07/2025).

Informed Consent: The committee waived the requirement for informed consent, as permitted by institutional and national regulations.

Conflict of Interest: The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

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Women Authorship in Cardiothoracic Surgery: Gender Differences in Five High-impact Journals Through 20 Years

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ABSTRACT

Objective: This study aimed to clarify the contribution of female authors to the cardiothoracic literature by analyzing five high-impact journals.

Materials and Methods: Two authors reviewed all articles from 2000, 2010, and 2020 published in five high-impact journals in the cardiothoracic discipline. Only original articles, reviews, and meta-analyses were enrolled in the study. During the review, the first author's name, the senior author's name, and the number of female and male authors were recorded according to years. Articles were also categorized according to subspecificity and region of study.

Results: A total of 233 papers in 2000, 259 papers in 2010, and 276 papers in 2020 met the study inclusion criteria. The ratio of female authors as first author was 4.3% in 2000, 8.9% in 2010, and 9.8% in 2020, and the difference was statistically higher in favor of 2010 and 2020 (p=0.041). The ratio of female authors increased from 24.9% in 2000 to 35.9% in 2020 (p=0.019). However, the ratio of senior female authors was not statistically significant (p=0.090). The ratio of female first authors for original articles and the ratio of female senior authors for reviews were significantly higher in 2010 and 2020. First female authors in papers about the heart and senior female authors in papers about the thorax were significantly more common in 2010 and 2020. Finally, the ratio of female first authors and senior authors significantly increased from 2000 to 2010 and 2020 only in Europe.

Conclusion: The present study demonstrated that the proportion of female authors significantly increased over the last 20 years in cardiothoracic surgery. First female authors made progress in articles written about experimental studies, original articles, and meta-analyses, and the heart. Finally, the frequency of female senior authors was significantly increased for experimental studies, review articles, papers about the thorax, and papers from Europe.

Keywords: Author, Cardiothoracic surgery, Female, Impact factor, Journal

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INTRODUCTION

Gender-related inequalities are still an important problem for women all over the world. Women are attempting to secure their rights in the field of health, as in all areas. Currently, 20–50% of the entire healthcare workforce comprises women, varying depending on region, social norms, and medical discipline.[1] However, women have been unable to gain an equal standing in certain fields, especially in surgical subspecialties, for several reasons, including gender discrimination, lack of female role models and mentors, and unconscious bias that questions women's surgical ability. Some studies have stated that women received less research funding, less sponsorship, and lower promotion rates in comparison to men.[2]

Previous studies showed that although the number of female health workers has increased, women are still underrepresented in scientific areas, including speaking at and/or chairing scientific congresses, working as educators in laboratory studies, and writing articles.[3] Scientific activities play a key role in promoting academic careers and getting scholarships. Whitley *et al*.[4] investigated the proportion of female authors in articles among five high-impact urology journals, and stated that the proportion of female authors increased from 18.9% in 2008 to 21.4% in 2018. Furthermore, Whitley et al.[4] emphasized that the frequency of the first author being female increased when the senior author was female. In another study, Filardo et al.[5] investigated the role of women as first authors in original articles among six high-impact journals, and the authors stated that the ratio of female authors increased from 27% to 37% between 1994 and 2014.

Although previous studies examined the contribution of women to academic articles in different disciplines, to our knowledge, no study investigated the proportion of female authors in cardiothoracic surgery studies. In the present study, we aimed to clarify the contribution of female authors to the cardiothoracic literature by analyzing five high-impact journals.

MATERIALS AND METHODS

The data collection and article review were conducted between July 1st and July 31st, and two authors reviewed all articles from 2000, 2010, and 2020 published in five high-impact journals in the cardiothoracic discipline. The journals were the Annals of Thoracic Surgery, Journal of Thoracic and Cardiovascular Surgery, European Journal of Cardiothoracic Surgery, Journal of Cardiac Surgery, and Thoracic Surgery Clinics. Online archives of the five journals were used during research. All five journals were published in 2000, in 2010, and in 2020. Despite a high impact factor in 2020, journals not published in either 2000 or 2010 were excluded. Furthermore, only original articles, reviews, and meta-analyses were enrolled in the study. Author replies, case reports, commentaries, expert opinions, and letters to the editor were excluded. We selected the years 2000, 2010, and 2020 to represent regular 10-year intervals across two decades, enabling the analysis of long-term trends while maintaining feasibility in data collection and validation.

During the review, the first author's name, the senior author's name, the number of authors, and the number of female and male authors were recorded according to year. Gender identification was primarily performed through publicly available information, including institutional profiles, research databases, and professional websites. When gender was not explicitly mentioned, it was inferred based on names and photographs when available. If gender could not be confidently determined, the article was excluded from the analysis. Furthermore, the author in single-author articles was accepted as the first author. In addition, all papers were categorized according to study type as a clinical trial or an experimental study. Articles were also categorized according to subspecificity (congenital, heart, and thorax) and region of study (Europe, America, and others).

First, we analyzed the ratio of female first authors and senior authors, and the proportion of all female authors in papers according to years for all journals. Furthermore, the first and senior female author ratio was compared according to journal, study type, article type, subspecificity, and region between 2000, 2010, and 2020.

This study analyzed publicly available published articles only and did not involve human participants or patient data. Therefore, ethics committee approval and informed consent were not required. This study did not involve human participants or patient-level data; therefore, informed consent was not required.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 22 (SPSS IBM Corp., Armonk, NY, USA) program was used. The Shapiro–Wilk test and Q-Q plots analysis were done to check the normality of variable distribution. Fisher's exact test and χ^2 test were used to compare categorical data. The statistical parameters were evaluated at 95% confidence level, and $p<0.05$ was considered statistically significant.

RESULTS

Impact factors of the reviewed journals are listed in Table 1. In total, 233 papers in 2000, 259 papers in 2010, and 276 papers in 2020 met the study inclusion criteria. The ratio of female authors as first author was 4.3% (10 papers) in 2000, 8.9% (23 papers) in 2010, and 9.8% (27 papers) in 2020, and

Table 1. Characteristics of the evaluated top 5 journals

Journal	Origin	Impact factor (2021)
The annals of thoracic surgery	The Netherlands	4.330
The journal of thoracic and cardiovascular surgery	USA	6.195
European journal of cardiothoracic surgery	United Kingdom	4.534
Journal of cardiac surgery	United Kingdom	1.620
Thoracic surgery clinics	The Netherlands	1.750

Table 2. Evaluation of female authors according to their order in the article and the years of the articles

	2000	2010	2020	*p*
First author, *n* (%)				
Male	223 (95.7)	236 (91.1)	249 (90.2)	
Female	10 (4.3)[a]	23 (8.9)[b]	27 (9.8)[b]	**0.041**
Total	233	259	276	
Senior author, *n* (%)				
Male	207 (95.4)	222 (93.7)	243 (90.3)	
Female	10 (4.6)	15 (6.3)	26 (9.7)	0.090
Total	217	237	269	
In any order, *n* (%)				
Male	175 (75.1)	171 (66.0)	177 (64.1)	
Female	58 (24.9)[a]	88 (34.0)[b]	99 (35.9)[b]	**0.019**
Total	233	259	276	

Lower-case letters are used to identify the group that causes the difference. The same letters (such as a-a) indicate that there is no difference, different letters (such as a-b) indicate that there is a difference

the difference was statistically significant in favor of 2010 and 2020 (p=0.041). In addition, the ratio of female authors increased from 24.9% in 2010 to 34.0% in 2010 and 35.9% in 2020 (p=0.019). However, though the ratio of senior female authors continuously increased from 2000 (4.6%) to 2010 (6.3%) and 2020 (9.7%), the difference was not statistically significant (p=0.090) (Table 1). Overall, female authorship is presented in Figure 1.

The ratio of first female author and senior author did not change for the Annals of Thoracic Surgery and Journal of Thoracic and Cardiovascular Surgery from 2000 to 2020. The ratio of first authors in the European Journal of Cardiothoracic Surgery and Journal of Cardiac Surgery was significantly higher in 2010 and 2020 than in 2000. In addition, the ratio

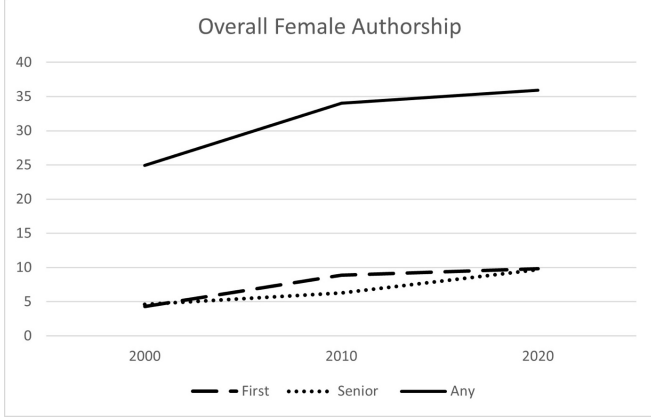

Figure 1. Overall female authorship.

of first authors in Thoracic Surgery Clinics was significantly higher in 2020 compared to 2000 and 2010. Furthermore, the ratio of senior authors was significantly higher in 2020 for the European Journal of Cardiothoracic Surgery and in 2010 and 2020 for thoracic surgery clinics. The ratio of female first and senior authors was not significantly different in 2000, 2010, and 2020 for clinical trials. However, the ratio of the first author was significantly higher in 2010 and 2020, and the ratio of the senior author was significantly higher in 2020 for experimental studies. The ratio of female first authors for original articles and the ratio of female senior authors for reviews were significantly higher in 2010 and 2020. Furthermore, the presence of a female author for meta-analysis papers was significantly more common in 2020. First female authors in papers about the heart and senior female authors in papers about the thorax were significantly more common in 2010 and 2020. Finally, the ratio of female first author and senior author significantly increased from 2000 to 2010 and 2020 only in Europe (Table 2). Table 3 shows a comparison of journal article characteristics and the percentage of female authors by region. The ratio of the total number of female authors to the total number of authors by years (separated by journals) and the ratio of the total number of female authors to the total number of authors by years (separated by regions) are presented in Figure 2a and b.

DISCUSSION

Providing women with equal opportunities is one of the most important issues of the last century. Revealing a problem with scientific data not only increases awareness of the problem but also contributes to efforts to solve the problem. Thus, we conducted a study that investigated the contribution of women to the cardiothoracic literature. The ratio of female first authors and the proportion of female authors significantly increased from 2000 to 2020. Furthermore, the ratio of first female

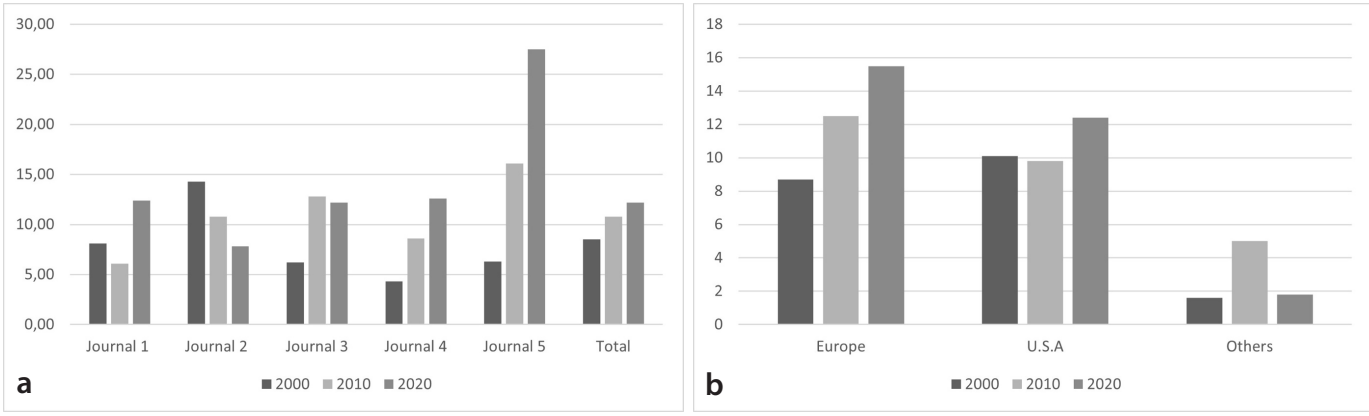

Figure 2. (a) The ratio of the total number of female authors to the total number of authors by years (separated by journals). **(b)** The ratio of the total number of female authors to the total number of authors by year (separated by regions)

Table 3. Comparisons of female author rates by journal, article features, and region

Journals	Percentage of female authors							
	First author				Senior author			
	2000	2010	2020	*p*	2000	2010	2020	*p*
1	4.5	6.0	8.1	*	5.6	4.4	10.0	*
2	9.7	7.8	8.9	*	7.4	3.2	5.5	*
3	2.9[a]	11.4[b]	8.3[b]	**	0[a]	3.8[a]	13.0[b]	**
4	0[a]	16.1[b]	6.1[b]	**	0	8.0	6.1	*
5	2.4[a]	5.7[a]	22.2[b]	**	4.3[a]	34.6[b]	24.2[b]	**
Study type								
Clinical trial	4.7	8.6	9.4	*	5.0	6.8	9.2	*
Experimental trial	3.2[a]	12.5[b]	18.0[b]	**	3.4[a]	6.7[a]	22.2[b]	**
Article type								
Original article	2.7[a]	6.3[b]	9.2[b]	**	5.5	3.7	7.7	*
Review	7.0	11.9	9.8	*	2.8[a]	10.4[b]	10.4[b]	**
Meta-analysis	0[a]	0[a]	16.7[b]	**	0	0	0	*
Sub-specificity								
Congenital	5.6	0	0	*	6.9	0	0	*
Heart	3.5[a]	11.5[b]	8.3[b]	**	5.2	2.4	7.4	*
Thorax	5.6	6.4	13.4	*	1.9[a]	10.8[b]	17.7[b]	**
Region								
Europe	2.0[a]	11.3[b]	10.9[b]	**	1.2[a]	7.1[b]	11.9[b]	**
America	7.0	7.8	11.6	*	10.2	7.6	10.8	*
Others	0	0	0	*	0	0	0	*

*$p>0.05$, **$p\leq0.05$. Lower-case letters are used to identify the group that causes the difference. The same letters (such as a-a) indicate that there is no difference, different letters (such as a-b) indicate that there is a difference.

authors significantly increased for experimental studies, for original articles and meta-analysis, for papers about the heart, and for papers from Europe from 2000 to 2020. In addition, the ratio of female senior authors significantly increased for experimental studies, for review articles, for papers about the thorax, and for papers from Europe.

Previous reports stated that women are much less involved in academic papers than men. Yue and Khosa analyzed the contribution of female authors in academic papers about orthopedic surgery, and the authors stated that women were underrepresented in terms of academic position and academic productivity.[6] In another study, Weiss *et al*.[7] demonstrated that only 2% of women were first and senior authors in urologic journals in 1974, with rates of 16.4% female first author rate and 8.5% senior author in 2009. Similarly, we found significant increments in female first-author and female total author rates from 2000 to 2020. In addition, our findings showed that female first authors for original articles and meta-analyses, and female senior authors for reviews, were significantly increased. The increased proportion of female first authors for original articles could be explained by the increased number of female physicians in cardiothoracic clinics, and the increased proportion of female authors for reviews could be explained by the increase in the number of women with academic positions.

The number of articles investigating women's inequality according to article type is limited. Vranas *et al*.[8] investigated 40 highly-cited journals between 2008 and 2018, and found that the percentage of female first authors was significantly higher for basic science papers compared to clinical studies. However, Vranas *et al*.[8] emphasized that the female senior author rate was similar for basic science articles. However, our findings demonstrate a clear upward trend in both female first and senior authorship in experimental studies between 2000 and 2020, suggesting a field-specific shift within cardiothoracic surgery.

The sociocultural development rate and the society's perspective on women can affect women's place in the health sector and their academic career. Vranas *et al*.[8] investigated the role of region on gender inequality in academic papers, and found the highest female first author rates in articles from Europe and New Zealand, and the lowest rates in articles from Asia. However, Pinho-Gomes *et al*.[9] reviewed papers about COVID-19 to analyze gender inequalities. Pinho-Gomes *et al*.[9] found the highest female author ratio in Oceania and the lowest in Africa, but the difference was not statistically significant. In the present study, we found that female first and senior author ratios significantly increased in 2010 and in 2020.

Our study has some limitations. First of all, there is a risk of gender misclassification and publication type misclassification. To minimize the possible misclassification, two independent authors analyzed articles, and they made a joint decision in case of conflict. Secondly, academic ranks of the authors (e.g., resident, specialist, associate professor, or full professor) could not be evaluated due to the unavailability of this information in most articles. This limitation may introduce potential bias in interpreting the true academic advancement of female authors, as authorship alone may not fully capture their academic position or progression. One of the limitations of this study is the selection of only three specific years at 10-year intervals. While this approach allowed us to capture long-term shifts in authorship trends and reduce data processing burden, it may have missed short-term fluctuations or unique trends in intervening years. Another limitation of our study lies in the methodology of gender classification. Gender was inferred using publicly available data, which may result in misclassification and excludes authors who identify outside the gender binary.

CONCLUSION

The present study demonstrated that the ratio of female authors significantly increased over the last 20 years in cardiothoracic surgery. Furthermore, our study showed that the first female authors made progress in articles written about experimental studies, original articles, and meta-analyses, and in papers from Europe over the last 20 years. Finally, the frequency of female senior authors was significantly increased for experimental studies, review articles, papers about the thorax, and papers from Europe.

DECLARATIONS

Ethics Committee Approval: This study analyzed publicly available published articles only and did not involve human participants or patient data. Therefore, ethics committee approval and informed consent were not required.

Informed Consent: This study did not involve human participants or patient-level data; therefore, informed consent was not required.

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The Effect of Pelvic Retroversion on Sagittal Balance and Clinical Outcomes

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ABSTRACT

Objective: Spinal disc degeneration and muscle atrophy with aging lead to reduced lumbar lordosis and sagittal imbalance. The body compensates by pelvic retroversion, which maintains posture but may increase disability despite preserved mobility. This study examined the relationship between pelvic retroversion and pain, disability, and quality of life in patients with low back pain.

Materials and Methods: A cross-sectional analysis was conducted on 122 patients presenting with low back pain. Patients with prior spinal surgery, advanced hip pathology, or major coronal deformities were excluded. Pain and disability were assessed using the Visual Analog Scale (VAS), Oswestry disability index (ODI), and Roland-Morris questionnaires. Standing full-length lateral radiographs were obtained to measure spinopelvic parameters. Pelvic retroversion was categorized according to the global alignment and proportion scoring system. Regression and correlation analyses were used to evaluate associations between radiological and clinical outcomes.

Results: The mean patient age was 43.5 years, and 47.6% exhibited pelvic retroversion. VAS scores did not differ significantly between retroversion groups. However, disability indices showed significant variation: Patients with severe retroversion demonstrated higher ODI scores, while those with mild retroversion had higher Roland-Morris scores compared with the balanced pelvis group. Multiple regression revealed that a balanced pelvis was associated with a 9-point lower ODI score. Negative correlations were observed between pelvic retroversion and both ODI (r_S=−0.31) and Roland-Morris scores (r_S=−0.28).

Conclusion: Pelvic retroversion, though a compensatory mechanism for sagittal imbalance, is more strongly associated with disability and quality of life than with pain severity. The results highlight the importance of evaluating pelvic tilt in low back pain patients, even in the absence of structural deformity. Routine radiographic assessment of pelvic parameters may identify individuals at risk for functional decline and guide timely preventive strategies.

Keywords: Pelvic retroversion, Quality of life, Sagital balance

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INTRODUCTION

With aging of the spine, multilevel disc degeneration, atrophy of the supporting erector muscles, and weakening of the ligamentous structures lead to a decrease in lumbar lordosis (LL).[1-4] Loss of LL disrupts sagittal balance, adversely affecting the patient's ability to stand upright, maintain gait stability, and preserve a forward gaze.[5]

Since the early 2000s, spinopelvic parameters have played a central role in the analysis of sagittal balance. While Roussouly classified lordosis and sacral orientation into types in the normal population, Schwab highlighted pelvic incidence (PI)-LL mismatch, pelvic tilt (PT), and sagittal vertical axis (SVA) as surgical targets with the adult deformity classification.[6-8] Le Huec formulated tilt and lordosis values based on PI, and Yilgör introduced the global alignment and proportion (GAP) score, providing a new perspective for patient-specific planning.[9,10] These findings demonstrate that pelvic measurements are not only morphological but are also closely related to functional outcomes in clinical practice.

Various compensatory mechanisms are developed by the body against sagittal imbalance.[9,11,12] The earliest and most effective of these is pelvic retroversion through an increase in pelvic tilt.[13,14] However, prolonged pelvic retroversion causes continuous contraction of the hip extensor muscles, leading to spasms and pain in the hip and hamstring muscles. In addition, it disrupts the three-dimensional joint configuration between the acetabulum and femoral head, accelerating the development of gonarthrosis.[15]

Pelvic retroversion is the primary compensatory mechanism that comes into play early in maintaining sagittal balance. However, its persistence may negatively affect hip biomechanics and may herald future spine–hip-related deformities.[16] Therefore, in pathologies that reduce lordosis, such as lumbar disc disease and spondylolisthesis, measurement of pelvic incidence, sacral slope, and pelvic tilt on standing plain radiographs is of clinical importance. The aim of this study was to investigate the relationship between the degree of pelvic retroversion and pain and quality-of-life scores in patients presenting with low back pain but without rigid sagittal imbalance.

MATERIALS AND METHODS

This study was approved by the Ankara Etlik City Hospital Institutional Review Board Committee (Date: 27.08.2025, Decision no: AEŞH-BADEK1-2025388). It was designed in accordance with the Declaration of Helsinki, and informed consent was obtained from all included patients.

Inclusion Criteria

- Presentation to the neurosurgery clinic with low back pain
- Age ≥18 years
- Ability to stand independently
- Mental status sufficient to complete standard questionnaires
- Clinical indication for obtaining standing scoliosis radiographs.

Exclusion Criteria

- Previous lumbar/hip/pelvic surgery
- Advanced hip pathology
- Lower extremity deformity: Knee flexion contracture >10°, leg length discrepancy >2 cm
- Neuromuscular diseases (e.g., Parkinson's disease, myopathy) and inflammatory spondyloarthritis/ankylosing spondylitis
- Presence of acute fracture, tumor, infection, or pregnancy
- Significant coronal deformity (e.g., Cobb ≥20°) or high-grade spondylolisthesis (e.g., Meyerding ≥II)
- Insufficient image quality on radiographic acquisition
- Epidural injection/major analgesic change within the past 4 weeks.

Demographic data, such as age and sex, as well as body mass index (BMI), were recorded. The visual analog scale (VAS) was used to assess the severity of back and leg pain. To evaluate the impact of low back pain on quality of life and disability, the Oswestry disability index (ODI) and the Roland-Morris disability questionnaire were administered.

Standing full-length lateral lumbar radiographs were evaluated using the hospital's picture archiving and communication system (PACS). Pelvic incidence was defined as the angle between the line drawn from the centers of the femoral heads to the midpoint of the S1 endplate and the line perpendicular to the S1 endplate. Sacral slope was defined as the angle between the S1 endplate and the horizontal plane; pelvic tilt as the angle between the line drawn from the centers of the femoral heads to the midpoint of the S1 endplate and the vertical plane. LL was calculated as the Cobb angle between the upper endplate of L1 and the upper endplate of S1. The SVA was recorded as the horizontal distance between a plumb line dropped from the midpoint of the C7 body and the posterosuperior corner of S1 (Fig. 1). All measurements were performed using the digital angle and distance tools available in the PACS system. In addition, to avoid measurement error in cases with very high or very low pelvic incidence, the degree of pelvic retroversion was calculated according to the GAP scoring system using the formula "sacral slope – (pelvic incidence × 0.59+9). According to this formula, values below

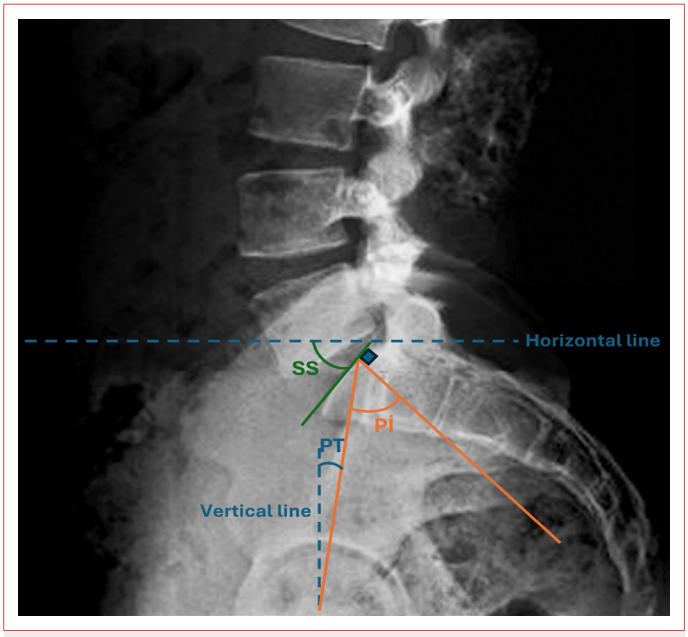

Figure 1. Radiological sssesment.
PI: Pelvic incidence, SS: Sacral slope, PT: Pelvic tilt

–15 were considered severe pelvic retroversion; between –15 and –7 moderate pelvic retroversion; between –7 and 5 balanced pelvis; and above 5 pelvic anteversion.[10]

Statistical Analysis

For four-group comparisons, the Kruskal–Wallis test was used due to non-normal distribution, and the Spearman correlation test was employed to evaluate relationships between two variables. To determine which independent variables (age, sex, occupation, BMI, and radiological parameters, etc.) affected the dependent variables (VAS, ODI, and Roland-Morris scores), univariate analyses were followed by multivariate logistic regression. For multivariate analyses, multiple linear regression was used, and overall model fit was assessed with the F test. The explanatory power of the model was expressed by the R^2 coefficient. Multicollinearity among variables was tested using the variance ınflation factor (VIF) values. Statistical analyses were performed using R Statistics. A $p<0.05$ was considered the threshold for statistical significance. Findings with p-values between 0.05 and 0.1 were interpreted as "marginal effects," assuming potential clinical relevance.

RESULTS

The mean age of the 122 patients included in the study was 43.5±14.5 years (min: 18 and max: 82). The mean height was 167.3±9.39 cm, weight 78.2±13.3 kg, and BMI 28.04±5.0 kg/m^2. Regarding spinal parameters, the mean LL angle was 56.6±13.3°, L4–S1 lordosis angle 35.3±9.8°, and SVA –VAs±38.5 mm. The mean GAP score was 3.2±2.8. Clinical measures were as follows: VAS score 6.99±2.15, ODI score 39.6±21.6, and Roland-Morris score 9.89±6.97 (Table 1).

Table 1. Descriptive analysis of continuous variables

Variable (*n*=122)	Mean	SD	Median	Min	Max	Range
Age	43.459016	14.549515	42.500	18.00	82.00	64.00
Height of the patient	167.286885	9.390059	166.500	150.00	188.00	38.00
Weight of the patient	78.180328	13.315011	78.500	48.00	120.00	72.00
BMI of the patient	28.038033	4.998066	28.000	19.13	45.70	26.57
Pelvic incidence	53.463934	13.138393	52.500	20.00	89.00	69.00
Sacral slope	33.101639	10.012554	33.000	7.00	55.70	48.70
Pelvic tilt	20.362295	11.506910	19.750	–4.00	53.00	57.00
Relative pelvic retroversion	–7.442082	8.801600	–6.385	–32.48	11.89	44.37
Lumbar lordosis angle	56.596721	13.259364	55.000	24.00	89.00	65.00
L4-S1 lordosis angle	35.336066	9.767005	35.000	12.00	60.00	48.00
Sagittal vertical axis (mm)	–7.470492	38.462676	–12.000	–83.00	178.00	261.00
Global tilt	14.449180	11.433858	11.000	–5.00	62.00	67.00
GAP score	3.204918	2.810660	3.000	0.00	13.00	13.00
VAS score	6.991803	2.145516	7.000	2.00	10.00	8.00
ODI score	39.639344	21.626455	38.000	0.00	96.00	96.00
Roland Morris	9.885246	6.970062	9.000	0.00	24.00	24.00

BMI: Body mass index, SD: Standard deviation, mm: Millimeter, GAP: Global alignment and proportion, VAS: Visual Analog Scale, ODI: Oswestry disability index.

Of the participants, 63.9% were female and 36.1% male. Regarding working conditions, 46.7% reported moderate, 26.2% severe, and 9.0% very severe working conditions. Radicular pain was present in 63.1%, while 32.8% had chronic comorbidities. With respect to pelvic parameters, mild retroversion was observed in 31.2% and severe retroversion in 16.4%. A balanced pelvis was found in 45.9% of participants, whereas anteversion was present in only 5.7% (Table 2).

Regression Analysis Models

Univariate analyses showed that several variables significantly affected VAS scores. Increasing height was associated with lower VAS scores (r=–rores $p<0.01$), indicating that taller individuals reported less pain. Among categorical variables, individuals with radicular pain reported significantly higher VAS scores (mean 7.30 vs. 6.47, $p=0.04$). Similarly, those with chronic comorbidities also reported higher VAS scores (7.75 vs. 6.62, $p<0.01$).

Table 2. Descriptive analysis of categorical variables

Variable	*n*	%
Gender		
Female	78	63.93
Male	44	36.07
The level of working condition		
Very severe	11	9.02
Severe	32	26.23
Moderate	57	46.72
Mild	14	11.48
Very mild	8	6.56
Existence of radicular pain		
No	45	36.89
Yes	77	63.11
Chronic comorbid disease		
No	82	67.21
Yes	40	32.79
Severe retroversion of pelvis		
No	102	83.61
Yes	20	16.39
Mild retroversion of pelvis		
No	84	68.85
Yes	38	31.15
Balanced pelvis		
No	66	54.10
Yes	56	45.90
Anteversion of pelvis		
No	115	94.26
Yes	7	5.74

In the multiple regression model predicting VAS scores, height and chronic comorbidities contributed at a marginal significance level. Each 1 cm increase in height decreased VAS by an average of 0.042 points (B=–Bintse $p=0.1$). The presence of chronic comorbidities increased VAS by an average of 0.76 points (B=0.762, p=0.1). Other variables showed no significant effect. The overall explanatory power of the model was 14% ($R^2=0.14$) and was statistically significant (F[4.117]=4.61, p=0.002). No multicollinearity was observed (VIF<2) (Table 3).

Several variables were significantly associated with ODI scores in univariate analyses. Age (r=0.33, p<0.001), BMI (r=0.27, p<0.01), and SVA (r=0.32, p<0.001) were positively correlated, whereas height (r=–right p<0.01) and L4–S1 lordosis angle (r =–rgles $p<0.001$) were negatively correlated. These findings indicate that age and spinal balance are closely related to disability levels. Among categorical variables, female sex, presence of radicular pain, presence of chronic comorbidities, and unbalanced pelvis were all associated with significantly higher ODI scores (all $p<0.05$).

In the multiple regression model for ODI, only the presence of a balanced pelvis had a significant effect. Individuals with a balanced pelvis had ODI scores that were on average 9.07 points lower (B=–Bwerse p<0.01). L4–S1 lordosis angle (negative) and radicular pain (positive) showed marginal associations (p=0.1). The overall explanatory power of the model was 28% ($R^2=0.28$), and the model was statistically significant (F[12,109]=3.55, $p=0.000$). No multicollinearity was found (Table 4).

Variables affecting Roland-Morris scores included age (r=0.26, p<0.01), SVA (r=0.28, p<0.01), and global tilt (r=0.19, p=0.04), all positively correlated, whereas height (r=–right p=0.01) and lumbar/L4–S1 lordosis angles were negatively correlated. This indicates that older individuals with postural imbalance experienced greater functional limitations. Among categorical variables, radicular pain, chronic comorbidities, mild pelvic retroversion, and unbalanced pelvis significantly increased Roland-Morris scores ($p<0.05$).

In the multiple regression model predicting Roland-Morris scores, no variable reached statistical significance, although some showed marginal effects. Each 1 mm increase in SVA increased functional impairment by 0.029 points ($p=0.1$). Radicular pain increased scores by an average of 1.99 points, and mild pelvic retroversion increased scores by an average of 2.78 points (both $p=0.1$). The explanatory power of the model was 21% ($R^2=0.21$), and the model was overall significant (F[10,111]=2.95, p=0.003). No multicollinearity was observed (Table 5).

Table 3. Full multivariate model - VAS_score

Predictor	B	SE	Beta (Standard)	*t*	*p*	VIF
(Intercept)	13.748	3.671		3.745	0.0***	
Height_of_patient	−0.042	0.021	−0.185	−1.972	0.1	1.19
Existance_of_radicular_pain Yes	0.493	0.410	0.111	1.201	0.2	
Chronic_comorbid_disease yes	0.762	0.408	0.167	1.870	0.1	
Balanced_pelvis yes	−0.551	0.381	−0.128	−1.444	0.2	

VAS: Visual analog scale, SE: Standard error, VIF: Variance ınflation factor. Model summary: R^2=0.14, Adj. R^2=0.11, F(4, 117)=4.61, p=0.002

Table 4. Full multivariate model – ODI score

Predictor	B	SE	Beta (Standard)	*t*	*p*	VIF
(Intercept)	75.633	55.331		1.367	0.2	
Age	0.193	0.174	0.130	1.109	0.3	2.074
Height_of_patient	−0.215	0.285	−0.093	−0.752	0.5	2.325
BMI_of_patient	0.248	0.430	0.057	0.576	0.6	1.499
Lumbar_lordosis_angle	0.042	0.191	0.026	0.219	0.8	2.074
L4_S1_lordosis_angle	−0.460	0.262	−0.208	−1.758	**0.1**	2.118
Sagittal_vertical_axscis	0.087	0.058	0.154	1.498	**0.1**	1.606
Global_tilt	0.028	0.223	0.015	0.124	0.9	2.111
GAP_score	−0.809	0.947	−0.105	−0.854	0.4	2.293
Gender male	−0.440	5.225	−0.010	−0.084	0.9	
Existance_of_radicular_pain yes	7.766	4.016	0.174	1.934	**0.1**	
Chronic_comorbid_disease yes	2.271	4.496	0.050	0.505	0.6	
Balanced_Pelvis yes	−9.070	4.435	−0.210	−2.045	**0.0***	

ODI: Oswestry disability index, SE: Standard error, VIF: Variance inflation factor, BMI: Body mass index, GAP: Global alignment. Model summary: R^2=0.28, Adj. R^2=0.20, F(12, 109)=3.55, p=0.000.

Table 5. Full multivariate model - roland_morris_score

Predictor	B	SE	Beta (Standard)	*t*	*p*	VIF
(Intercept)	21.154	13.712		1.543	0.1	
Age	0.042	0.055	0.087	0.764	0.4	1.821
Height_of_patient	−0.067	0.072	−0.090	−0.929	0.4	1.330
Lumbar_lordosis_angle	−0.054	0.062	−0.103	−0.873	0.4	1.952
L4_S1_lordosis_angle	−0.006	0.086	−0.009	−0.074	0.9	2.021
Sagittal_vertical_axscis	0.029	0.019	0.160	1.522	0.1	1.556
Global_tilt	−0.027	0.069	−0.045	−0.394	0.7	1.801
Existance_of_radicular_pain Yes	1.994	1.324	0.139	1.507	0.1	
Chronic_comorbid_disease Yes	0.898	1.499	0.061	0.599	0.6	
Mild_retroversion_of_pelvis Yes	2.785	1.668	0.186	1.670	0.1	
Balanced_pelvis Yes	−0.849	1.604	−0.061	−0.529	0.6	

SE: Standard error, VIF: Variance inflation factor. Model summary: R^2=0.21, Adj. R^2=0.14, F(10, 111)=2.95, p=0.003.

Table 6. Comparison between groups according to relative pelvic tilt

	Severe retroversion	Mild retroversion	Balanced pelvis	Anteroversion pelvis	*p*
VAS score	7.15±2.43	7.45±2.04	6.59±2.12	6.86±1.68	*p*=0.3397[1]
ODI score	46.60±22.22	45.11±22.76	34.18±20.03	31.71±16.14	***p*=0.002**[1]
Rolland Morris score	9.25±6.87	12.82±7.33	8.11±5.97	8.29±7.70	***p*=0.043**[1]

VAS: Visual Analog Scale, ODI: Oswestry disabilty index. [1]Krukal–Wallis test. *Post hoc* Dunn test for ODI: The differences were between severe retroversion and balanced pelvis (*p*=0.0051) and between severe retroversion and anteversion (*p*=0.0078). *Post hoc* Dunn test for Roland-Morris: Difference was between the mild retroversion and the balanced pelvis group (*p*=0.0006).

Comparison of Pelvic Retroversion Groups

Comparison of ODI scores across pelvic retroversion groups showed significant differences (p=0.0020). *Post hoc* Dunn's test indicated that the differences were between severe retroversion and balanced pelvis (*p*=0.0051) and between severe retroversion and anteversion (*p*=0.0078) (Table 6). Comparison of Roland-Morris scores across groups also showed significant differences (*p*=0.043). *Post hoc* Dunn's test revealed that this difference was between mild retroversion and the balanced pelvis group (*p*=0.0006) (Table 6).

No significant differences were found in VAS scores across pelvic retroversion groups (Table 6). Spearman correlation analysis revealed no significant correlation between pelvic retroversion and BMI or VAS (*p*=0.44, p=0.08). However, pelvic retroversion was negatively correlated with ODI (rs=–sshel *p*=0.00054) and Roland-Morris scores (rs=–ssres p=0.0013).

DISCUSSION

Pelvic retroversion is one of the earliest compensatory mechanisms against sagittal imbalance and is defined as posterior rotation of the pelvis through an increase in pelvic tilt.[17-19] With the decrease in LL, the individual retroverts the pelvis to maintain upright posture and forward gaze, thereby rebalancing the SVA.[9] Although this adaptation stabilizes posture in the short term, continuous activation of the hip extensor muscles in the long term may cause muscle fatigue, hamstring spasms, and alterations in joint biomechanics.[20] As a result, even in the absence of rigid deformity, patients may experience disability and reduced functional capacity.[21]

In this study, the clinical implications of pelvic retroversion were investigated in patients with low back pain but without rigid sagittal deformity. The findings showed that pelvic retroversion was not directly associated with pain severity (VAS) (*p*=0.08), but significantly affected quality of life and functional capacity. Patients with severe retroversion had significantly higher ODI scores compared with those with a balanced pelvis (*p*=0.0051) and anteversion (*p*=0.0078) (*p*=0.0020 overall). Similarly, a significant difference in Roland-Morris scores was observed between the mild retroversion and balanced pelvis groups (*p*=0.0006; overall p=0.043). Multivariate regression analysis showed that having a balanced pelvis reduced ODI scores by 9 points (B=–Bintsd p<0.01). In addition, correlation analyses revealed significant negative associations between the degree of pelvic retroversion and both ODI (rs=–sshov *p*=0.00054) and Roland-Morris scores (rs=–ssres p=0.0013). These results support the hypothesis that pelvic retroversion is an early compensatory mechanism for sagittal imbalance and has serious negative effects on disability and quality of life rather than on pain itself.

With the widespread use of magnetic resonance imaging (MRI), patients presenting with spinal complaints, such as low back pain often undergo lumbar MRI.[22-24] However, as MRI scans are performed in the supine position, parameters, such as pelvic tilt and LL may be misinterpreted.[25,26] For example, a patient with hypolordotic lumbar spine in the standing position may appear to have normal lordosis on supine MRI.[27] Therefore, standing lumbar radiographs – which are more accessible and cost-effective than MRI – remain critically important in evaluating patients with low back pain, though they have been neglected by many spine surgeons in recent years. With the development of MRI technology, upright MRI scans will likely be increasingly used to assess spinopelvic parameters; however, this technique is still available only in a limited number of centers worldwide.[28,29]

In patients with high PT, acetabular tilt, anteversion, and external coverage increase, whereas anterior acetabular coverage angles decrease significantly, as demonstrated by Assi *et al*.[30] These changes disrupt load distribution on the acetabular cup, concentrating greater force on a smaller surface area, thereby predisposing to gonarthrosis and impingement. Hirata *et al*.[31] showed that preoperative posterior pelvic tilt in patients undergoing hip surgery negatively affected postoperative gait speed and quality-of-life measures. In a review by Morimoto on hip–spine syndrome, spinopelvic parameters, such as pelvic incidence and pelvic tilt, were shown to influence load distribution on the acetabular cup.[32]

Kellis reported that hip extensor muscles were stronger in patients with anterior pelvic tilt compared with those with posterior tilt.[33] This may suggest that in sagittal imbalance, pelvic compensation is linked to hamstring fatigue and overuse.

In Assi's study, an increase in PT negatively affected ODI scores but had no significant effect on short form 36 (SF-36) physical component summary or SF-36 mental component summary scores.[30] In the 222-patient series by Yilgor *et al*.,[21] relative pelvic version (RPV) – also used in our study – showed a stronger correlation with deterioration in ODI, core outcome measures index, SF-36, and scoliosis research society-22 scores compared with PT. They emphasized that PT is reliable only in patients with pelvic incidence close to the normal range, whereas RPV, as an individualized measure, is more dependable. Yiming Fan reported that degenerative spine patients with pelvic tilt >18.4° were 3.1 times more likely to require surgical intervention than those with pelvic tilt <18.4°, highlighting PT as a determinant in surgical decision-making.[34] Won-Deuk Kim, in a controlled study of office workers with low back pain, found that those with pelvic tilt imbalance had poorer muscle endurance, reduced hip mobility, and worse quality-of-life indices.[35]

Limitations

As computed tomography scans were not performed, 3D reconstructions could not be obtained, and measurements were made using two-dimensional radiographs. The observer dependency of radiological measurements makes standardization difficult. The absence of long-term follow-up limited the ability to monitor dynamic changes, leaving the study cross-sectional. Moreover, only static measurements were available, and dynamic spinopelvic parameters during gait could not be assessed.

Strengths

The main strength of this study is its focus on the clinical implications of pelvic retroversion before the development of rigid deformity, addressing a patient group relatively underexplored in the literature. Another strength is the use of validated questionnaires (VAS, ODI, Roland-Morris) to link pelvic retroversion not only to morphological changes but also to functional outcomes. The relatively large sample size (n=122) for a single-center study further increases the statistical power of the results.

CONCLUSION

This study demonstrated that in patients with low back pain without rigid deformity, pelvic retroversion is associated more with functional capacity and quality of life than with pain. The finding that severe retroversion led to deterioration in ODI and Roland-Morris scores suggests that pelvic retroversion may represent not only an important early compensatory mechanism of sagittal balance but also a precursor of progressive deformity. Therefore, in the evaluation of patients presenting with low back pain, routine consideration of pelvic tilt and RPV measurements is of great clinical importance.

DECLARATIONS

Ethics Committee Approval: This study was approved by the Ankara Etlik City Hospital Institutional Review Board Committee (Date: 27.08.2025, Decision no: AEŞH-BADEK1-2025388).

Informed Consent: Informed consent was obtained from all included patients.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – OKD; Design – OKD, MIO; Supervision – CE, HKK; Materials – FHE; Data collection and/or processing – FHE, CE; Analysis and/or interpretation – CE, MIO.; Literature review – OKD; Writing – OKD; Critical review – CE, HKK.

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ORIGINAL ARTICLE

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Functional Outcomes and Discomfort Following Different Treatment Modalities for Rockwood Type III Acromioclavicular Joint Injuries

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ABSTRACT

Objective: There is no consensus for the optimal treatment method for Rockwood type III acromioclavicular (AC) injuries. The aim of the study is to compare treatment methods in terms of functional scores and patient discomfort.

Materials and Methods: In this retrospective cohort study, patients with Rockwood type III AC joint injuries treated either conservatively or surgically between 2022 and 2024 were evaluated. Patients were categorized based on treatment modality (conservative vs. surgical) with an exploratory subgroup analysis comparing hook plate and suture-button fixation within the surgically treated cohort. The QuickDASH scores and results of a questionnaire evaluating overall discomfort rates, activities provoking discomfort, and presence of persistent pain were compared between the groups after a 12-month follow-up period.

Results: A total of 53 patients (age 39.2±12.7, 79.2% male) were evaluated. A total of 21 patients (39.6%) were treated conservatively and 32 (60.4%) surgically, including 15 with hook plate and 17 with suture-button fixation. Conservative and surgery groups showed no statistically significant differences in median QuickDASH scores (p=0.235) or questionnaire results (p>0.05) at 12 months postoperatively. In the exploratory subgroup analysis, no significant differences could be detected between median QuickDASH scores of hook plate and suture-button groups (p=0.165); however, patient-reported overall discomfort was higher in the hook plate group (60% vs. 23.5%, p=0.036).

Conclusion: In Rockwood type III AC joint injuries, no statistically significant differences in functional outcomes were observed between conservative and surgical treatments. Exploratory subgroup analysis suggested an association between hook plate fixation and higher rates of patient-reported discomfort compared with suture-button fixation.

Keywords: Acromioclavicular joint injuries, Fracture fixation, internal, Patient-reported outcome measures, Shoulder injuries, Treatment outcome

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INTRODUCTION

Acromioclavicular (AC) joint injury refers to injuries that can damage the AC and coracoclavicular (CC) ligaments following high- or low-energy trauma.[1,2] This injury accounts for 10–40% of all shoulder injuries and is more common in young individuals who engage in active sports.[3] It is important for young adults to return to sports and work as early as possible.[4] For this reason, various treatment methods have been defined to restore the function of the AC joint.[5]

Injuries ranging from sprains to complete tears of the AC and CC ligaments are present. The Rockwood classification,[6] established in 1984, guides orthopedic surgeons in the treatment of AC joint injuries based on injuries of the AC and CC ligaments, the degree of clavicular displacement, and the direction of displacement as determined by direct X-rays.[7] Reviewing the current literature, it is widely accepted that conservative treatment is suitable for type I and II injuries, and type IV to VI injuries should be treated surgically.[8-10]

Rockwood type III AC joint injuries are defined as rupture of both ligaments (AC and CC), and there is displacement of 25–100% compared to the contralateral CC distance.[3,6,7] Although there are efforts to guide treatment,[11] there is a controversy on whether Rockwood type III AC injuries should be treated conservatively or surgically. While some authors state that conservative treatment is more successful in terms of cosmetic appearance, long-term clinical outcomes, and complications in type III AC joint injuries, other authors argue that surgery should be performed because it allows the CC distance to return to normal, enables early rehabilitation after surgery, and yields good early clinical outcomes.[3,10-13]

In the surgical treatment of AC joint injuries, suture-button[3,10,14] and hook plate[3,10,15] are the most preferred methods. The suture-button system is more frequently preferred in athletes due to reasons such as causing less tissue damage, not requiring implant removal, and mimicking the flexibility of normal ligaments.[14] The hook plate system's ability to provide a more stable reduction is its most important advantage, while its tendency to cause subacromial irritation and the need for implant removal constitute its limitations.[16] While there is ongoing debate in the current literature regarding the application of surgical or conservative treatment in type III AC joint injuries, there is also no agreement on the choice between hook plate or suture-button.[5,15,17-20]

The primary objective of this retrospective cohort study was to evaluate differences in patient-reported outcomes between conservative and surgical management of type III AC joint injuries. A secondary, exploratory objective was to assess patient-reported outcomes between suture-button and hook plate fixation within the surgically treated cohort. It was hypothesized that treatment modality would be associated with differences in patient-reported outcomes and discomfort.

MATERIALS AND METHODS

This study was conducted after obtaining ethical approval from Ankara Etlik City Hospital Clinical Research Ethics Committee (date: 06.08.2025, decision no: AEŞH-BADEK1-2025-335). The requirement for informed consent was waived due to the retrospective nature of the study. This study was performed following the ethical framework of the Declaration of Helsinki.

In this retrospective cohort study aiming comparison of different surgical treatment modalities, the patient information of those who presented to our hospital's orthopedics and traumatology department due to AC joint injuries from September 2022 to September 2024 was retrospectively reviewed. Inclusion criteria were type III AC joint injury, age 18–65, diagnosis and treatment in the acute phase (first 3 weeks) after injury, and a minimum follow-up period of 12 months. Criteria for exclusion were: Presentation later than 3 weeks, history of fracture in the ipsilateral extremity, surgical treatment with methods other than suture-button or hook plate, vascular or nerve damage after injury, additional surgical interventions (like revision or wound debridement), previous treatment for any shoulder conditions, additional diseases that could affect the evaluation of questionnaires (neuromuscular disease, psychiatric disease, speech and communication difficulties, rheumatological disease), patients who did not want to participate in the study, or patients who did not attend their 1-year follow-up appointment. Fifty-three patients were enrolled after exclusion. Figure 1 demonstrates the study flowchart.

Surgery and Treatment Protocol

The treatment and follow-up of all patients included in the study were performed by orthopedic and traumatology specialists experienced in trauma at a training hospital or by their assistants under specialist supervision. Treatment decisions were based on routine clinical judgment considering patient characteristics and injury-related factors; however, due to the retrospective design, these factors could not be systematically quantified.

Conservative Treatment

Patients who underwent conservative treatment were followed up with a simple arm sling. As the patients' pain decreased, passive and then active joint movement was initiated. Patients were instructed to use their current bandage or arm sling for at least 4 weeks. All patients undergoing conservative treatment were informed that deformity or swelling may remain in the AC joint and that chronic dislocation may lead to persistent pain, instability, and osteoarthritis in the AC joint.

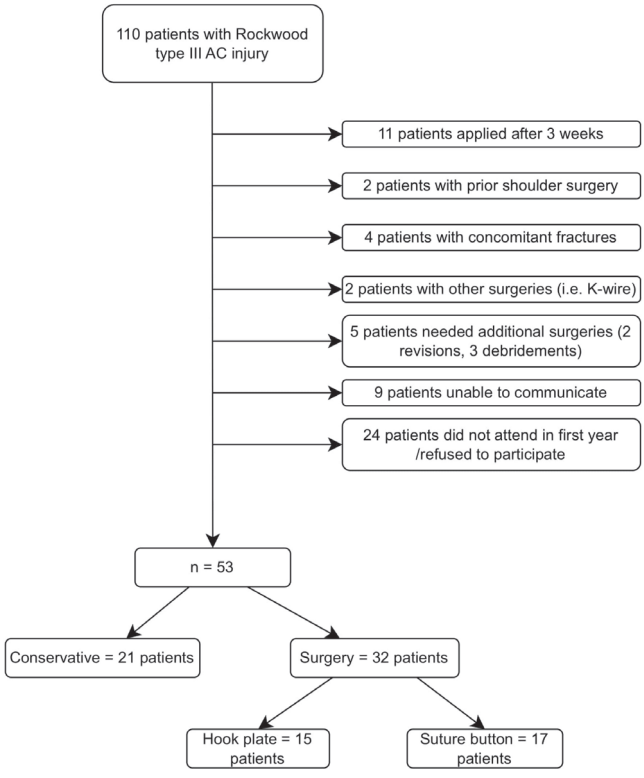

Figure 1. Study flowchart.

Suture-Button Fixation

All patients were administered 1 g of cefazolin under general anesthesia while in the supine position, followed by a 5–6 cm incision over the AC joint. After reduction of the AC joint under direct visualization, an entry site for a suture-button (Aleda, Ankara, Türkiye) was created using a 4.0 mm drill bit from the clavicle toward the base of the coracoid. Using a passing pin, the button was passed through the clavicle and coracoid. After ensuring that the implant had passed through the coracoid, the strands of the suture-button were pulled tight. After a fluoroscopy check, a locked knot was tied, and the surgery was completed. The patients' shoulders were immobilized with a sling for 3–4 weeks after surgery (Fig. 2).

Hook Plate

After administration of 1 g of cefazolin to all patients, under general anesthesia, in the supine position, a 5–6 cm incision was made over the AC joint. The AC joint was exposed and anatomically reduced. After reduction, an anatomical hook plate (Zimed, Gaziantep, Türkiye) was placed in the subacromial space. It was then fixed to the clavicle using cortical and locking screws. After the reduction of the AC joint, the position of the plate and hook, and the screw lengths were checked under fluoroscopy, and the surgery was completed. All patients were encouraged to use an arm sling for 4–6 weeks after surgery. No routine or elective implant removal was performed, and all hook plates remained in situ throughout the follow-up period, including at 12 months (Fig. 3).

Outcome Measures

Patients were invited for a 1-year follow-up visit, and for those who were admitted, besides the QuickDASH score,[21,22] a simple questionnaire was performed. This questionnaire consisted of three questions:

- Do you have any discomfort due to the injury?
- What provokes this discomfort the most?

1. Tasks requiring shoulder motion

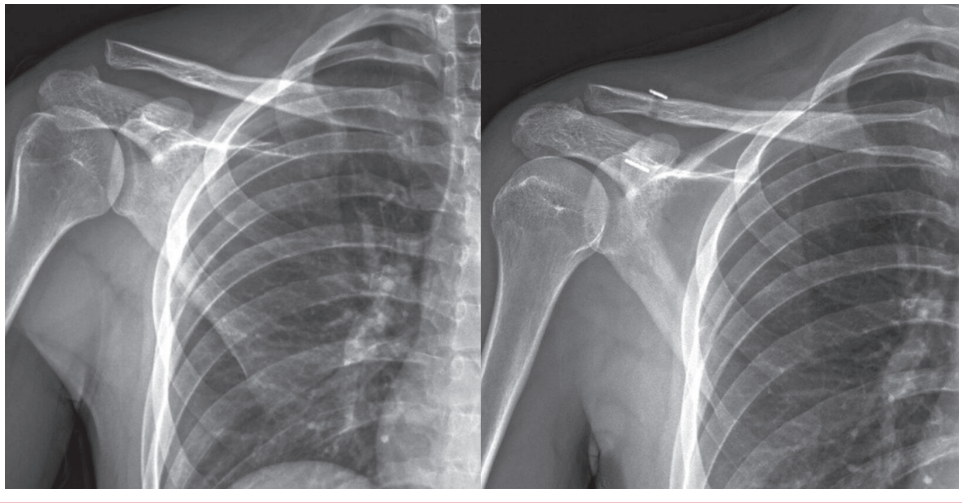

Figure 2. Pre-operative and post-operative X-rays of a 34-year-old male who presented with Rockwood type III acromioclavicular injury, treated with suture-button.

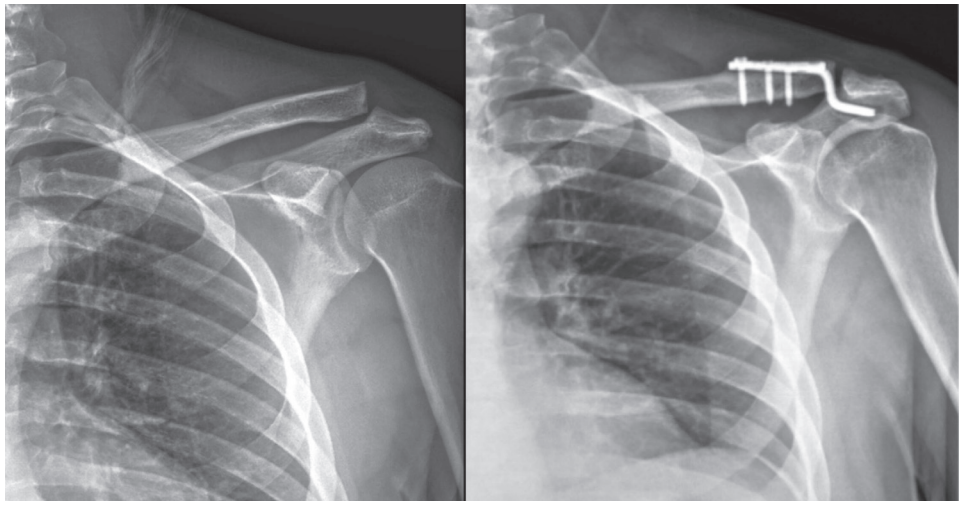

Figure 3. Pre-operative and post-operative X-rays of a 45-year-old male presented with Rockwood type III acromioclavicular injury, treated with hook plate.

2. Lifting heavy things
3. Lying on the injured side

- Did you apply to the hospital due to pain in the last 3 months?

The demographic characteristics of all patients (age, sex, and body mass index [BMI]), dominant side, involvement of the dominant side, QuickDASH scores, and questionnaire results were compared between the conservative and surgical treatment groups to assess baseline comparability and potential confounding effects. In addition, in surgically treated patients, the same parameters, as well as time from injury to surgery, were analyzed and compared between the hook plate and suture-button groups. Subgroup analyses comparing hook plate and suture-button fixation were performed in surgically treated patients and were considered exploratory, without pre-specified hypotheses. Selection bias is possible due to the retrospective design and surgeon preference for treatment modality. To reduce this effect, baseline characteristics were compared and found to be similar between groups.

Statistical Analysis

Statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) 26.0 (SPSS Inc., Chicago, Illinois, USA). Normality of the data was analyzed with the Shapiro–Wilk test. Age and BMI conformed to normal distribution, while time to surgery and QuickDASH score did not. Numerical data were reported as mean ± standard deviation or median (Q1-Q3), and frequency and percentage were reported for categorical data. Differences between numerical values were compared by an independent sample t-test and Mann–Whitney U test. Chi-square test or Fisher's exact test was used for categorical data. Potential confounders, including age, sex, BMI, and dominance-related variables, were assessed by comparing baseline characteristics between groups. Multivariable adjustment was not performed due to the limited sample size. No a priori sample size calculation was performed due to the retrospective nature of the study. $p<0.05$ was accepted as statistically significant.

RESULTS

A total of 110 patients were assessed for eligibility. After applying the inclusion and exclusion criteria, 53 patients (age 39.2±12.7, 79.2% male) were included in the final analysis. Demographic data were presented in Tables 1 and 2. 21 patients (39.6%) were treated conservatively, and 32 patients (60.4%) were treated surgically (15 patients with a hook plate and 17 patients with a suture button). No significant difference could be found in terms of demographic data between conservative and surgery-treated groups and between surgery types ($p>0.05$).

The mean QuickDASH score of the study cohort was 0 (0–18.2). 19 patients (35.8%) had discomfort in the injured shoulder. Among these patients, 12 (63.2%) reported that this discomfort was provoked by tasks requiring shoulder motion, 1 (5.3%) by lifting a weight, and 6 (31.5%) by lying on the injured side. 7 patients (13.2%) were admitted to the hospital in the last 3 months due to pain from the injury site.

Thirty-three patients had the injury on their dominant sides (62.3%). No statistically significant difference could be detected in terms of QuickDASH scores ($p=0.795$) and questionnaire results ($p>0.05$) between patients with dominant and non-dominant side injuries.

Conservative Versus Surgery

No significant difference could be detected in terms of QuickDASH score (p=0.235) and questionnaire results (p>0.05) (Table 1).

Hook Plate Versus Suture Button

An explanatory analysis was performed among the surgically treated patients. Median time from injury to surgery was 3 (1–5) days. No significant difference could be detected between hook plate and suture button groups in terms of time to surgery (p=0.165) (Table 2).

No significant difference could be detected between QuickDASH scores of hook plate and suture button groups (p=0.165). However, overall discomfort was reported to be higher in the hook plate group (60–23.5% – absolute difference: 36.5%, p=0.036). No statistically significant differences were detected between groups for the remaining questionnaire items (p>0.05).

Table 1. Comparison of demographic data and study results between conservatively and surgically treated groups

	Conservative (n=21) (%)	Surgery (n=32) (%)	p
Age	39.5±14.4	39±11.6	0.895 [1]
Sex (male)	17 (81)	25 (78.1)	0.804 [2]
Body mass index	25.7±4	27.4±4.4	0.167 [1]
Dominant hand (right)	17 (81)	26 (81.3)	0.978 [2]
Injury to dominant side	14 (66.7)	19 (59.4)	0.592 [2]
Median QuickDASH score (Q1-Q3)	0 (0–11.4)	0 (020.5)	0.235 [3]
Discomfort?	6 (28.6)	13 (40.6)	0.371 [2]
Activity provoking discomfort			
Shoulder motion	4 (66.7)	8 (61.5)	
Lifting weight	0 (0)	1 (7.7)	0.902 [4]
Lying on the same side	2 (33.3)	4 (30.8)	
Admission in the last 3 months	2 (9.5)	5 (15.6)	0.690 [4]

[1] Independent samples t-test; [2] Chi-square test; [3] Mann–Whitney U test; [4] Fisher's exact test.

Table 2. Comparison of demographic data and study results between hook plate and suture button groups

	Hook plate (n=15) (%)	Suture button (n=17) (%)	p
Age	39.5±11.4	38.5±12.1	0.811 [1]
Sex (male)	13 (86.7)	13 (76.5)	0.659 [2]
Body mass index	27.2±5.9	27.6±2.8	0.834 [1]
Dominant hand (right)	11 (73.3)	15 (88.2)	0.383 [2]
Injury to dominant side	9 (60)	10 (58.8)	0.946 [3]
Time to surgery	2 (1–3.5)	3 (2–7)	0.165 [4]
Median QuickDASH score (Q1-Q3)	18.2 (0–20.5)	0 (0–9.1)	0.168 [4]
Discomfort?	9 (60)	4 (23.5)	0.036 [3]
Activity provoking discomfort			
Shoulder motion	5 (55.6)	3 (75)	
Lifting weight	1 (11.1)	0 (0)	0.175 [2]
Lying on the same side	3 (33.3)	1 (25)	
Admission in the last 3 months	3 (20)	2 (11.8)	0.645 [2]

[1] Independent samples t-test; [2] Fisher's exact test; [3] Chi-square test; [4] Mann–Whitney U test

DISCUSSION

Rockwood type III AC joint injuries continue to be a subject of debate, both regarding the choice between conservative and surgical management and the optimal surgical technique. In this study, we revisited this frequently investigated topic – typically evaluated in terms of complications and functional outcomes – from the perspective of patients' subjective complaints. As a result, we were unable to determine the superiority of surgical treatment over conservative treatment. However, we found a higher discomfort rate in patients who underwent hook plate surgery compared to those who underwent suture-button fixation.

Dislocations of the AC joint, which are mainly caused by the disruption of static stabilizers (AC and CC ligaments),[18] mostly occur due to direct lateral impact on the adducted shoulder,[23,24] and are commonly seen in young males[25] that involve in sports or traffic accidents.[26] Yearly incidence of AC joint injuries is 19.3/100,000,[25] and a substantial ratio of these injuries present at a late stage.[27]

Among the classification systems for guiding treatment and reporting purposes, the most widely used is the Rockwood classification.[11,24] For Rockwood types I and II, conservative treatment (with a simple arm sling) is the main choice of treatment, and surgery is often recommended for types IV to VI to avoid long-term complications.[24] However, treatment modality for type III is controversial, and the choice of treatment mainly depends on the surgeon's preference. Surveys among orthopedic surgeons about the management of these injuries reveal that the global trend is to follow these injuries conservatively.[28,29]

Conservative treatment of type III AC injuries, such as milder ones, includes a simple arm sling for 3–4 weeks and then allowing active arm motion. In a study comparing brace and sling immobilization, no significant difference was found between the two modalities.[30] Our opinion is that a sling is a simpler method to comply with the patients, therefore arm sling was preferred for conservative treatment.

In our study, we could not detect a statistically significant difference in terms of median QuickDASH scores and questionnaire outcomes between conservative and surgery groups. Many studies reported good outcomes following conservative treatment for type III AC injuries. A meta-analysis investigating 10 studies comparing conservative and surgical treatment showed that conservative treatment showed similar outcomes compared to surgical treatment, with fewer complications.[31] Similarly, in a recent multicenter randomized controlled study by Tauber et al.,[32] surgical treatment yielded slower functional recovery compared to conservative treatment. There are several studies reporting less persistent pain[33] and better overall outcomes[5] with surgical treatment, although the latter[5] included type V injuries, which were not included in our study. Although not statistically significant, persistent pain (demonstrated by admission to hospital due to pain in the last 3 months) (9.5–15.6%) and overall discomfort (28.6–40.6%) appeared less in the conservatively treated group.

There are several surgical techniques for the treatment of AC joint injuries. The most widely used methods include hook plate and suture-button fixation, which were evaluated in our study. One of the most remarkable findings of our study was that hook plate fixation resulted in significantly more discomfort than suture-button, although no statistically significant difference was detected in terms of QuickDASH scores and other questionnaire results. This finding is consistent with existing studies.[5,15,17-19] The focused issues about the inferior results of hook plate fixation in the literature is need for secondary surgery and subacromial osteolysis.[20] While our study did not specifically investigate the reasons behind the inferiority of hook plate fixation, we believe that placing a hardware component directly within the joint may contribute to a certain degree of irritation. Cosmetic concerns and chronic alterations in the AC architecture are areas for future research. It should be noted that suspensory loop devices, such as suture-button needs a correct tunnel placement in order to prevent complications.[34]

The QuickDASH score is an adaptation of the DASH score and one of the most common scoring systems in shoulder disorders. Unlike the Constant–Murley score, it is solely dependent on patients' answers and does not involve examination findings. Therefore, it can be considered a good indicator for the impact of the pathology on the patient's comfort,[21,22] therefore complying with the aim of our study. However, the main issue about this scoring system is that it has a high ceiling effect – i.e., diminished ability to discriminate between high levels of function.[35] Therefore, in addition to the QuickDASH score, a questionnaire that aimed to investigate the most prevalent complaints about follow-up of AC joint injuries (persistent pain, presence of discomfort, and the activity that provoked the discomfort) was applied to the patients, and it allowed us to reveal that the hook plate group had a higher discomfort rate than the suture-button fixation group.

In addition to its retrospective design, this study has several limitations. First, this was a single-center study, which may limit the generalizability of the findings to other clinical settings. Given the relatively small sample size, the study may be at increased risk of Type II error, particularly for functional outcome measures. Borderline P-values observed in some comparisons raise the possibility that clinically meaningful

differences may not have been detected due to insufficient statistical power. Furthermore, patients were treated and followed by multiple surgeons, which may have introduced variability in treatment selection; however, this also enhances the external validity of the results within a real-world clinical context. The lack of standardization in treatment choice may have allowed residual confounding to persist despite comparable baseline characteristics. Another limitation is the absence of radiological measurements. Radiological assessment was beyond the scope of this study, and it should be noted that parameters such as CC distance would be expected to be greater in conservatively treated patients, as no reduction was performed. The absence of routine hook plate removal may have contributed to higher patient-reported discomfort and should be considered when interpreting comparisons with other series in which elective plate removal is standard practice. Finally, the three-item questionnaire used to assess discomfort is an institution-specific, non-validated tool, and its psychometric properties, including validity and reliability, are unknown. Therefore, results derived from this questionnaire should be interpreted with caution. Although no validated instrument specifically addressing this aspect of discomfort in AC joint injuries is currently available, this limitation should be considered when interpreting the findings.

CONCLUSION

In patients with Rockwood type III AC joint injuries, no significant differences were observed in QuickDASH scores or overall patient discomfort between conservative and surgical treatment groups. However, among the surgical techniques, patients treated with hook plate fixation reported a higher rate of overall discomfort compared to those who underwent suture-button fixation. Despite this difference in subjective discomfort, no statistically significant difference in functional outcomes as measured by QuickDASH scores was detected between the two surgical methods.

Ethics Committee Approval: This study was approved by the Ankara Etlik City Hospital Clinical Research Ethics Committee (Date: 06.08.2025, Decision no: AEŞH-BADEK1-2025-335).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

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Authorship Contributions: Concept – EBD, FB; Design – FB; Supervision – FB; Resource – FB; Materials – EBD; Data collection and/or processing - EBD; Analysis and/or interpretation – FB; Literature review – EBD; Writing - FB, EBD; Critical review – FB, EBD.

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Scapular Notching Remains a Clinically Relevant Radiographic Finding in Reverse Shoulder Arthroplasty

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ABSTRACT

Objective: To evaluate the frequency of scapular notching and its association with functional outcomes following reverse shoulder arthroplasty (RSA).

Materials and Methods: This retrospective study included 83 patients with a minimum follow-up of 36 months who underwent RSA at a tertiary care center between 2010 and 2019. Radiographs were evaluated for scapular notching according to the Sirveaux classification. Clinical outcome assessment was based on pre- and post-operative results with the University of California–Los Angeles [UCLA] score and the American Shoulder and Elbow Surgeons (ASES) score, while pain was evaluated with the Visual Analog Scale (VAS). Patients were classified for the presence or absence of scapular notching.

Results: Scapular notching was detected in 46 patients (55.4%). All patients demonstrated significant post-operative improvement in UCLA, ASES, and VAS scores ($p<0.001$). However, patients without notching had significantly higher post-operative UCLA (27 vs. 25, $p=0.027$) and ASES scores (82 vs. 72, $p=0.007$) compared to those with notching. The magnitude of improvement (score change) in UCLA was also greater in the non-notching group (22 vs. 17, $p<0.001$). The groups were similar in terms of post-operative VAS scores and the decline in pain.

Conclusion: Scapular notching is a common complication following RSA and, despite overall clinical improvement, is associated with less favorable functional outcomes compared with patients without notching.

Keywords: Functional outcomes, Implant design factors, Reverse shoulder arthroplasty, Scapular notching, Sirveaux classification

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INTRODUCTION

Reverse shoulder arthroplasty (RSA) is now widely used for the management of complex shoulder pathologies, most notably rotator cuff arthropathy. In cases where conventional anatomical prostheses fail to provide satisfactory outcomes, RSA improves the biomechanical efficiency of the deltoid muscle in arm elevation, which improves function and clinical outcomes.[1,2] Despite its utility, RSA is associated with a number of clinically-relevant complications. The most frequently reported include instability, infection, scapular notching, mechanical failure, nerve injury, fracture, and component disassembly.[3] Among these, scapular notching arises from mechanical impingement between the scapular neck and the humeral component, which is due to altered biomechanics introduced by the prosthesis.[4,5]

Some clinicians consider scapular notching not as a complication in itself but as a characteristic finding after RSA[6] (Fig. 1). Regardless of how it is interpreted, scapular notching is most commonly detected radiographically within the first 6 months after surgery, with a prevalence ranging from 4.6% to 96%.[4] Multiple factors contribute to its development, with implant selection, component positioning, and patient-specific anatomical variations being the most critical.[7] The effect of scapular notching on functional outcomes, prosthesis stability, and patient satisfaction remains controversial. While some studies suggest an association with reduced function and increased risk of revision surgery, others have reported no significant influence on clinical results.[8-10] Further studies are therefore required to clarify its mid/long-term clinical implications.

We designed the present study as a midterm follow-up of patients who underwent RSA in a tertiary care hospital, with a focus on determining the prevalence of scapular notching and to evaluate its relationship with established outcome measures, including the University of California at Los Angeles Shoulder Score (UCLA), the American Shoulder and Elbow Surgeons Score (ASES), and the Visual Analog Scale (VAS). The aim was to explore whether scapular notching should be considered only radiographic or a clinically relevant complication. We hypothesized that the presence of scapular notching would be associated with inferior functional outcomes.

MATERIALS AND METHODS

Study Design and Ethical Approval

This investigation was conducted as a single-center retrospective cohort study. It involved a review of clinical and radiological follow-up data from patients who underwent RSA at the Department of Orthopedics and Traumatology, Gazi University Faculty of Medicine, between 1 January 2010 and 31 December 2019. Ethical approval was obtained from the Ethics Committee of Gazi University Faculty of Medicine (date: 31.12.2024, decision no: 2024–2003), and all procedures were carried out in accordance with the principles of the Declaration of Helsinki.

Patient Selection

The study population consisted of patients who underwent RSA and had attended at least 3 years of clinical follow-up. Inclusion criteria were: Older than 18 years, undergoing primary surgery with an indication for RSA, and having complete records of pre-operative and follow-up assessments of functional and pain scores, including UCLA, ASES, and VAS. We excluded patients who had undergone revision surgery, cases treated with RSA due to tumor(s), individuals with neuromuscular disorders, those who underwent bilateral

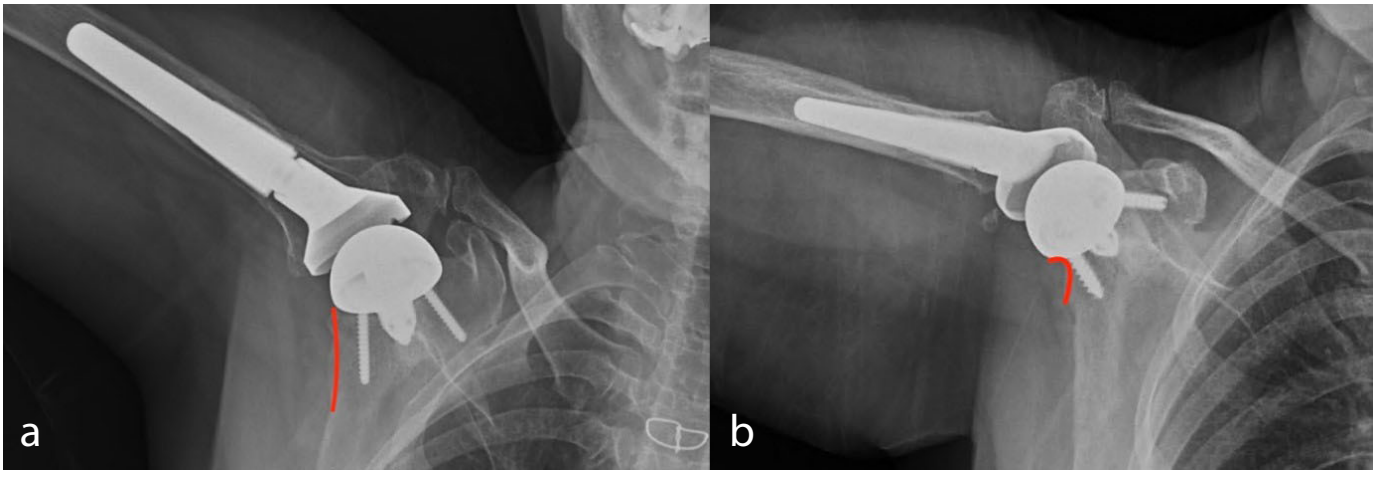

Figure 1. (a) Patient without a scapular notching, **(b)** Patient with a scapular notching.

procedures, and subjects with incomplete radiological follow-up. Ultimately, 83 patients who met the eligibility criteria were included in the analysis.

Surgical Approach and Rehabilitation

All patients underwent RSA (SMR, Lima, Italy) through a standard deltopectoral approach performed by the same orthopedic team. The primary objective of the procedure was to restore glenoscapular balance and to achieve implant positioning that would optimize deltoid muscle function. Whenever feasible, the subscapularis tendon was preserved and reattached. For glenoid component placement, an inferior position was preferred, with particular attention to maintaining adequate clearance between the inferior margin of the glenosphere and the inferior cervical border of the scapula. Following post-operative pain control, pendulum and passive range of motion exercises were initiated, with active range of motion exercises introduced after the 1st week. The rehabilitation program was tailored to each patient and carried out under physiotherapist supervision, with return to sports allowed between weeks 8 and 12.

Radiological Assessment

All post-operative shoulder radiographs were obtained digitally from the hospital archives, and for each patient included in the study, control radiographs taken at a minimum of 3 years post-operatively were evaluated. To avoid duplication, only the longest available follow-up images for each patient were included in the analysis. Assessments were performed independently by two orthopedic surgeons using standardized anteroposterior (true AP) and axillary views. The images were reviewed through the Picture Archiving and Communication System, and scapular notching was graded according to the Sirveaux classification. In cases of disagreement, a consensus evaluation was reached with the involvement of a third orthopedic surgeon. The degree of scapular notching was classified from 0 (none) to 4 (severe). For the primary comparison, patients were grouped as either without notching (grade 0) or with notching (grade ≥1).[11]

Clinical Assessment and Data Collection

In our clinic, patients undergoing RSA have routinely been evaluated for many years using the VAS, UCLA, and ASES at each pre- and post-operative follow-up visit, with results recorded in their medical files. For this study, clinical scores documented pre-operatively and at the final follow-up visit (minimum 3 years post-operatively) were retrieved retrospectively from the hospital archive system. Functional outcomes were assessed using Turkish validated UCLA and ASES, while pain was evaluated using VAS.[12,13] For each patient, the change between pre- and post-operative values was also calculated. All scores were derived from data recorded by the treating physician during in-person visits and documented in medical charts.

The ASES score, developed by the ASES, combines both patient-reported and clinician-assessed components, with a maximum of 100 points. In this study, we analyzed the patient-reported component, which consists of a 10 cm VAS for pain (50 points) and ten Likert-type items addressing functional capacity in activities of daily living (50 points).[13,14]

The UCLA shoulder score assesses five domains: Pain, function, active range of motion (forward flexion), muscle strength, and patient satisfaction. Each domain has its own score range, and the total score is calculated on a 35-point scale.[12,15] These assessments were performed during outpatient visits by non-surgical members of the orthopedic team through face-to-face evaluations and were documented accordingly. Both UCLA and ASES scores were applied pre-operatively and at the final follow-up. Changes between the 2 time points were also calculated.

Pain levels were evaluated using the VAS, consisting of a 10 cm horizontal line on which patients were asked to indicate their average pain intensity. A score of zero (0) represented "no pain," whereas ten (10) corresponded to "unbearable pain." Patients marked their perceived pain levels both pre-operatively and at the final follow-up. Scores were then measured in centimeters and converted into numerical values. All assessments were carried out at the bedside under the direct supervision of the trained clinical team.

Statistical Analysis

We used the IBM Statistical Package for the Social Sciences software (v27.0) to collect data and obtain descriptive and statistical analysis results (IBM Corp., Armonk, NY, USA). For statistical analyses, the classic *P* value threshold of <0.05 was defined as the threshold for significant results. Parametric assumptions were assessed (histogram, Q-Q plots, etc.). Descriptive statistics are presented using mean±standard deviation for normally distributed continuous variables, and with median (25th percentile - 75th percentile) for non-normally distributed continuous variables. Between groups, comparisons of continuous variables were performed using the Student's t test or Mann–Whitney U test, depending on the normality of distribution. Pre- and post-operative comparisons of scores were performed using the Wilcoxon signed-rank test due to non-normality of distribution. Categorical descriptives (nominal, ordinal) were reported as frequency (count, *n*) and percentage (column %). Between-groups comparisons of categorical variables were performed using the chi-square test or Fisher-Freeman-Halton test.

RESULTS

A total of 83 patients who underwent RSA were included in the study. Scapular notching was identified in 46 patients (55.42%), while 37 patients (44.58%) did not exhibit any notching. The overall age range was 26–88 years. Patients with scapular notching were significantly older than those without notching (66.41±11.05 vs. 61.22±11.68 years; p=0.041). No significant differences were observed between the groups regarding sex distribution, side of surgery, arm dominance, surgical indication, or follow-up duration (p>0.05 for all). The median follow-up duration for the entire cohort was 72 months (interquartile range [IQR]: 48–84 months), with a follow-up range of 37 to 117 months (Table 1).

Functional Outcomes

All 83 patients showed individual gains in functional scores (UCLA, ASES) and reductions in pain scores (VAS) following surgery. The median UCLA score improved from 6 (IQR: 5–8) pre-operatively to 26 (IQR: 23–30) post-operatively (p<0.001). The ASES score increased from 22 (IQR: 16–33) to 75 (IQR: 70–85) (p<0.001), while the VAS score decreased from 8 (IQR: 8–9) to 2 (IQR: 1–2) (p<0.001).

When stratified by scapular notching status, both groups showed significant improvements in UCLA, ASES, and VAS scores post-operatively (p<0.001 for all within-group comparisons). However, post-operative UCLA scores were significantly lower in the notching group compared to the non-notching group (median 25 vs. 27; p=0.027, Fig. 2). A

Table 1. Summary of patients' characteristics with regard to groups

	Total (*n*=83) (%)	Scapular notching		*p* (between groups)
		Present (*n*=46) (%)	Absent (*n*=37) (%)	
Age at surgery, years, mean±SD	64.10±11.56	66.41±11.05	61.22±11.68	**0.041**†
Sex				
Male	17 (20.48)	9 (19.57)	8 (21.62)	1.000§
Female	66 (79.52)	37 (80.43)	29 (78.38)	
Side				
Right	43 (51.81)	27 (58.70)	16 (43.24)	0.238§
Left	40 (48.19)	19 (41.30)	21 (56.76)	
Dominance				
Dominant arm	58 (69.88)	33 (71.74)	25 (67.57)	0.864§
Non-dominant arm	25 (30.12)	13 (28.26)	12 (32.43)	
Indication				
Primary glenohumeral arthritis	31 (37.35)	15 (32.61)	16 (43.24)	0.603¶
Proximal humerus fracture	23 (27.71)	14 (30.43)	9 (24.32)	
Failed osteosynthesis	11 (13.25)	6 (13.04)	5 (13.51)	
Massive irreparable rotator cuff tears	8 (9.64)	6 (13.04)	2 (5.41)	
Failed hemiarthroplasty	6 (7.23)	2 (4.35)	4 (10.81)	
Post-instability arthropathy	4 (4.82)	3 (6.52)	1 (2.70)	
Follow-up time, months	72 (48–84)	72 (60–84)	60 (48–84)	0.127‡
Sirveaux classification				
Grade 1	36 (43.37)	36 (78.26)	-	N/A
Grade 2	7 (8.43)	7 (15.22)	-	
Grade 3	3 (3.61)	3 (6.52)	-	
Grade 4	0 (0.00)	0 (0.00)	-	

Descriptive statistics are presented using mean±standard deviation for normally distributed continuous variables, median (25th percentile–75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. † Student's *t* test, ‡ Mann–Whitney U test, § Chi-square test, Fisher-Freeman-Halton test. Statistically significant p values are shown in bold. N/A, Non-applicable.

similar difference was observed in post-operative ASES scores (median 72 vs. 82; p=0.007, Fig. 3). No significant difference was found in post-operative VAS scores between the two groups (median 2 vs. 1; p=0.782).

In terms of score changes, the increase in UCLA score was greater in patients without scapular notching (median 22 [IQR: 19–25] vs. 17 [15–21]; p<0.001). This difference in improvement was also replicated for ASES scores, albeit not reaching statistical significance (median 57 [45–65] vs. 49 [42–57]; p=0.074). The reduction in VAS scores was also comparable between groups (median –7 [–8 to –6] vs. –6 [–8 to –4]; p=0.275) (Table 2).

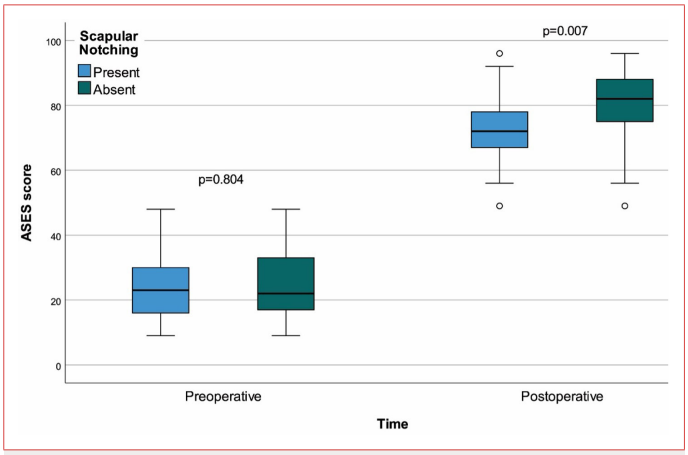

Figure 2. Box plots of the University of California–Los Angeles score with regard to scapular notching.

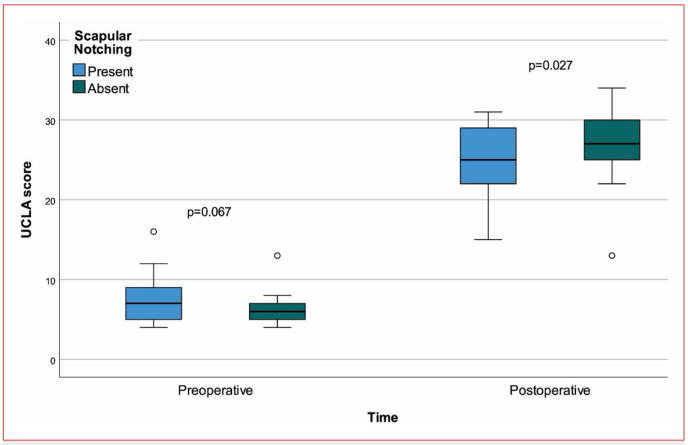

Figure 3. Box plots of American Shoulder and Elbow Surgeons score with regard to scapular notching.

Table 2. Summary of pre-operative and post-operative scores with regard to groups

	Scapular notching			
	Total (*n*=83)	**Present (*n*=46)**	**Absent (*n*=37)**	***p* (between groups)**
UCLA score				
Preoperative	6 (5–8)	7 (5–9)	6 (5–7)	0.067‡
Post-operative	26 (23–30)	25 (22–29)	27 (25–30)	**0.027**‡
p (within groups)	**<0.001**#	**<0.001**#	**<0.001**#	
Change [1]	20 (17–24)	17 (15–21)	22 (19–25)	**<0.001**‡
ASES score				
Pre-operative	22 (16–33)	23 (16–30)	22 (17–33)	0.804‡
Post-operative	75 (70–85)	72 (67–78)	82 (75–88)	**0.007**‡
p (within groups)	**<0.001**#	**<0.001**#	**<0.001**#	
Change [1]	52 (42–60)	49 (42–57)	57 (45–65)	0.074‡
VAS score				
Pre-operative	8 (8–9)	8 (7–9)	9 (8–9)	0.265‡
Post-operative	2 (1–2)	2 (1–2)	1 (1–2)	0.782‡
p (within groups)	**<0.001**#	**<0.001**#	**<0.001**#	
Change[1]	–6 (–8––5)	–6 (–8––4)	–7 (–8––6)	0.275‡

Descriptive statistics are presented using median (25th percentile–75th percentile) for non-normally distributed continuous variables. (1) Difference between post- and pre-operative, positive values represent an increase, and negative values represent a decrease. ‡ Mann–Whitney U test, # Wilcoxon signed ranks test. Statistically significant *p* values are shown in bold. UCLA: University of California-Los Angeles; ASES: American Shoulder and Elbow Surgeons; VAS: Visual analog scale.

DISCUSSION

Despite its efficacy in rotator cuff insufficiency and glenohumeral joint degeneration, RSA has procedure-specific complications that may influence long-term clinical outcomes and patient satisfaction. In the present study, the prevalence of scapular notching and its relationship with clinical outcomes were evaluated in patients treated with RSA, demonstrating that scapular notching is a common condition. Furthermore, although both functional and pain scores improved significantly in all patients, functional scores were found to be impacted by the presence of scapular notching.

The fact that scapular notching persists as a clinically relevant despite advances in surgical techniques and implant design is an important finding for practitioners of this surgery. In the present study, the observed notching rate was 55.4%. The wide range of prevalence reported in the literature (4.6–96%) has classically been associated with surgical technique, implant selection, patient anatomy, and imaging methodology,[6,7,16] the latter of which might indicate that the detection of this condition can be impacted by improper imaging or inconsistent definitions. Systematic reviews describe a more conservative estimate of 12% and 52% depending on prosthesis design, which could be associated with the advances in implants and their configurations,[17,18] especially since modern designs reduce the incidence of notching compared to traditional inlay components, with rates as low as 15%.[19] Inferior placement, lateralization of the glenosphere, and the inclination angle of the humeral component are known to influence the risk of contact between the scapular neck and the humeral implant. For instance, a large long-term cohort study demonstrated that the incidence of notching exceeded 70% in implants with a 155° neck–shaft angle, whereas prostheses with a 145° angle showed significantly lower frequency.[20] Notching is also understood as a dynamic process that can develop with progressive changes in the implant (polyethylene wear) and bone structure (osteolysis).[21,22] Over time, both the frequency and the reported significance of notching appear changed. A systematic review indicated that prevalence ranged from 35.4% to 47.1% before 2010, but decreased to 22.5% after this cut-off, most likely due to improved implant designs and increasing surgical experience.[23] In addition to implant factors, patient-related variables, such as body mass index have also been associated with notching.[24] Furthermore, mechanical impingement between the humeral component and the scapula during extension, adduction, and external rotation has been implicated as a contributor to inflammation and prosthetic loosening.[2] Nevertheless, the relatively short follow-up durations and potential selection bias in many studies could be obfuscating the true prevalence. While our results show the continuing relevance of scapular notching in RSA and its association with functional outcomes, the lack of detailed implant data in our study prevented implant-specific analyses.

The potential impact of scapular notching on functional recovery after RSA has long been debated. In our cohort, although all patients showed post-operative improvement, those with notching demonstrated significantly lower post-operative UCLA and ASES scores compared with patients without notching. Moreover, the improvement in UCLA score was also significantly less in patients with notching, suggesting that notching may limit functional gains. Our findings are consistent with systematic reviews and meta-analyses, which have clearly shown that scapular notching exerts a clinically relevant negative effect on functional scores, including shoulder range of motion, flexion, and abduction.[10] Several previous studies have similarly demonstrated adverse effects of notching on range of motion and clinical outcomes at midterm follow-up.[11,25-27] Conversely, a smaller number of studies have reported no significant association between post-operative notching and either function or pain.[28,29] Differences in follow-up duration, implant design, assessment methods, and patient heterogeneity could each explain the differing interpretations regarding this topic. Taken together, we believe that our results support the majority of the literature in classifying scapular notching as a clinical problem that impacting function rather than a purely radiographic phenomenon. Accordingly, minimizing the risk and severity of notching would appear to be crucial to improving functional outcomes.

In our study, a significant post-operative reduction in VAS scores was observed in both patients with and without notching, and both groups appeared to experience similar magnitudes of improvement. This indicates that the functional impact of scapular notching does not reflect on perceived pain intensity. The association between notching and pain remains controversial in the literature.[30] Several studies have failed to demonstrate a link between high rates of notching and increased pain levels.[8,31] Conversely, other series have reported associations between notching, pain, functional decline, and even early aseptic loosening.[9,29,30] Pain perception is known to vary considerably between individuals, and multiple factors, including implant conformity, capsular tension, deltoid adaptation, medications, and even post-operative behavioral adjustment to minimize pain, may contribute to reported pain levels. Based on the present results, we believe that scapular notching is largely unassociated with pain severity.

The retrospective design of this study limits data collection to availability and record accuracy, which prevents analysis of other factors associated with notching or functional outcomes. The presence and grading of scapular notching were assessed

visually on standard radiographs. Although this modality is widely used for diagnostic purposes even when other methods are readily-available, it is possible that diagnostic accuracy would have been improved by more sensitive and quantitative imaging methods (computed tomography or magnetic resonance imaging). The relatively small sample size was arrived upon due to strict inclusion and exclusion criteria. We believe this was necessary for unconfounded analyses; however, statistical analysis comparing different notching grades were not possible. Pain was evaluated using VAS, which is inherently subjective, and potential confounders were not controlled. Finally, detailed technical information regarding prosthesis configuration, including implant type, surgical technique, glenosphere size, and component positioning, was not consistently available in the retrospective records, preventing further analysis of these parameters.

CONCLUSION

Scapular notching is a common complication following RSA and, despite overall clinical improvement, is associated with less favorable functional outcomes compared with patients without notching.

DECLARATIONS

Ethics Committee Approval: This study was approved by the Gazi University Faculty of Medicine Ethical Committee (Date: 31.12.2024, Decision no: E-1130153).

Informed Consent: All participants consented to participate in the study.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – TE, EBO, MAT, UK, AEY; Design – TE, EBO, A.E.Y.; Supervision – TE, MAT, EBO; Data Collection and/or Processing – EBO, BB; Analysis and/or Interpretation – EBO, BB, MAT, AEY; Literature review – TE, BB, MAT; Writing – TE, EBO, MAT, UK; Critical Review – BB, UK.

Peer-review: Externally peer-reviewed.

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First-trimester Ferritin as a Predictor of Postpartum Transfusion: A Retrospective Cohort Study

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ABSTRACT

Objective: Iron deficiency is the most common nutritional deficiency in pregnancy and a key contributor to maternal anemia and postpartum transfusion. However, no consensus exists regarding optimal screening strategies or ferritin thresholds for early detection in non-anemic women. To evaluate whether first-trimester maternal ferritin levels predict postpartum blood transfusion in non-anemic pregnant women and to establish population-specific ferritin cut-off values for transfusion risk.

Materials and Methods: This retrospective study included 386 singleton pregnancies followed and delivered at a tertiary university hospital between September 2022 and February 2024. Women with first-trimester hemoglobin (Hb) ≥11 g/dL were eligible. Patients with hemorrhage-related complications, hemoglobinopathies, or early iron therapy were excluded. Maternal demographic and laboratory parameters and neonatal outcomes were retrieved from electronic records. Receiver operating characteristic analyses were performed to determine optimal first-trimester thresholds for predicting postpartum transfusion.

Results: According to World Health Organization criteria (ferritin <15 µg/L), 29% of women were iron-deficient; using the 30 µg/L criterion, 66.6% showed depleted iron stores. Postpartum anemia occurred in 43%, and 8% required transfusion. Patients who required transfusion were significantly older and had higher parity (p=0.019 and <0.001, respectively). Median first-trimester ferritin was 22.65 µg/L. Optimal predictive threshold was 19.6 µg/L for ferritin (Area under the curve =0.634; p=0.012). In multivariable analysis, parity independently predicted transfusion (Odds ratio [OR]=1.85, p=0.001), while ferritin showed a borderline inverse association (OR=0.98, p=0.056). No significant association was observed between first-trimester ferritin and composite neonatal outcomes.

Conclusion: First-trimester ferritin <19 µg/L identifies women at increased risk of postpartum transfusion, even when Hb is normal. Routine ferritin screening in early pregnancy could enhance patient blood-management strategies by enabling timely detection and treatment of subclinical iron deficiency.

Keywords: Anemia, Blood transfusion, Ferritins, First trimester, Iron deficiency, Pregnancy trimester

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INTRODUCTION

Iron deficiency is the most common nutritional disorder worldwide and remains the leading cause of anemia in both high-income and resource-limited settings.[1] Its prevalence among pregnant women varies substantially, ranging from 20% to 90%, depending on geographic, socioeconomic, and healthcare access-related factors.[2,3] Women of reproductive age are particularly vulnerable due to menstrual blood loss and the markedly increased iron requirements of pregnancy. Because childbirth inherently carries the risk of significant blood loss, optimizing maternal iron status during gestation is essential to improve maternal outcomes and reduce the need for peripartum transfusion.

Iron deficiency and iron deficiency anemia (IDA) in pregnancy have well-documented adverse effects on both mother and fetus. In mothers, IDA has been associated with fatigue, impaired cognitive and physical performance, increased susceptibility to infections, heightened risk of peripartum hemorrhage, cardiovascular strain, greater transfusion requirements, and prolonged hospital stays. For the fetus, maternal iron deficiency has been linked to preterm birth, intrauterine growth restriction, impaired placental development, and reduced neonatal iron stores.[4-6]

Despite the recognized burden of iron deficiency, no universal consensus exists regarding optimal screening, diagnostic thresholds, or management strategies during pregnancy. While hemoglobin (Hb)-based anemia screening is widely implemented, standardized guidance for detecting non-anemic iron deficiency remains absent. Routine ferritin testing in the first trimester is not currently recommended in clinical practice, and treatment algorithms for patients with low ferritin are lacking. Furthermore, discrepancies in defining iron deficiency particularly ferritin cut-off values ranging from <10 µg/L to <30 µg/L, with the World Health Organization (WHO) recommending <15 µg/L – combined with the absence of pregnancy-specific reference ranges, complicate clinical decision-making.[7-10]

The present study aimed to determine whether first-trimester maternal ferritin levels can predict the need for postpartum blood transfusion, a major contributor to maternal morbidity and prolonged hospitalization. And also, we evaluated the association between early pregnancy iron status and neonatal outcomes. In the second part, we aimed to determine population-specific cut-off values for ferritin, Hb, and hematocrit (Hct) were established to predict transfusion requirements.

MATERIALS AND METHODS

This study includes pregnant women who were followed during pregnancy and delivered at University Hospital setting between September 01, 2022, and February 01, 2024. This is a tertiary referral center with approximately 1,000 births/year. Ethical approval for this study was obtained from the Lokman Hekim University Scientific Research Ethics Committee (Date: 28.03.2024, Approval No: 2024/89). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Pregnancies in which a positive fetal heartbeat was detected by sonography during the first trimester whose ferritin and Hb levels were measured at their first visit, and who completed antenatal follow-up and delivery at our clinic were enrolled in the study. First-trimester ferritin levels were below 15 µg/L were classified as the iron-deficiency group as defined by a threshold of 15 µg/L ferritin by WHO. In addition, regarding the WHO guideline criterion for anemia (Hb levels <11 g/dL in the first TRIMESTER), only patients with Hb levels ≥11 g/dL at the first trimester were included in the study. In addition, guidelines such as those issued by the American College of Obstetricians and Gynecologists and the National Institute for Health and Care Excellence consider a ferritin level of 30 µg/L as the diagnostic cut-off for iron deficiency.

Patients with conditions that could lead to excessive bleeding during delivery – such as placenta previa, postpartum atony, multiple pregnancy, placental abruption, or placenta percreta – were excluded from the study. In addition, patients with known thalassemia or other hemoglobinopathies, as well as those who delivered at another facility, were also excluded. Individuals who had received any form of iron supplementation, including oral preparations or intravenous replacement, during the first trimester were excluded from the analysis.

Each pregnant participant underwent complete blood count (hemogram) testing at both the beginning of the second and third trimesters. Patients with Hb levels <10.5 g/dL in the second trimester or <11 g/dL in the third trimester were started on oral ferrous sulfate therapy, which was continued throughout the remainder of pregnancy. Hemogram assessments were repeated 4 weeks after initiation of treatment. Pregnant women who were unable to tolerate oral iron, whose anemia did not improve with oral therapy, or who remained anemic within 4 weeks of the expected delivery were administered ferric carboxymaltose.

In the postpartum period, blood transfusion was administered to patients with Hb levels <7 g/dL or to those exhibiting clinical symptoms (such as tachypnea, tachycardia, or hypotension) in conjunction with a decline in hemogram values. Intravenous ferric carboxymaltose was given to asymptomatic patients with Hb levels <10 g/dL in the postpartum period.

Clinical and laboratory data of the patients retrospectively reviewed using the hospital's electronic medical record system. Information regarding maternal age, body mass index (BMI), obstetric history, and first-trimester Hb, Hct, and ferritin levels was collected. Mode of delivery, peripartum complications, postpartum Hb and Hct levels, and the need for blood transfusion were assessed. Neonatal birth weight, appearance, pulse, grimace, activity, respiration (APGAR) scores, Hb, and Hct levels were recorded. Apgar score <7, intrauterine growth restriction, preterm labor, and fetal distress were classified under the composite adverse neonatal outcome.

The primary goal of this study is to analyze the relationship between first-trimester ferritin levels and the need for postpartum blood transfusion, as well as the association between ferritin levels and neonatal outcomes. The secondary outcome was to determine the population-specific cut-off values for ferritin, Hb, and Hct to predict the likelihood of transfusion requirements.

RESULTS

A total of 386 patients were included in the study. According to the first-trimester ferritin cut-off values of WHO, 112 patients (29%) were identified as having iron deficiency. If the ferritin cut-off value of 30 µg/L is applied, 257 women (66.6%) in the first trimester can be identified as having depleted iron stores.

The median age of the participants was 28 years (min-max: 19–42), the median BMI was 24 kg/m^2 (min-max: 17–42), and the median parity was 1 (min-max: 0–5). The first-trimester laboratory results revealed the median Hb and Hct levels as 12.6 g/dL (min-max: 11–15.3) and 37.5% (min-max: 30.6–44.5), respectively. For ferritin, the median value was calculated as 22.65 µg/L (min-max: 2.4–155).

During pregnancy, 18 patients (4.5%) were administered ferric carboxymaltose in the third trimester, and 243 patients (63%) received oral iron supplementation during the second or third trimester. Postpartum anemia was observed in 166 patients (43%). A total of 32 patients (8%) required postpartum transfusion, while 7 patients (1.8%) received ferric carboxymaltose in the postpartum period.

When comparing demographic parameters (age, BMI, and parity) between patients with and without a history of postpartum transfusion, statistically significant differences were observed in age and parity (p=0.019 and p<0.001, respectively) (Table 1).

The median gestational age at delivery was 38 weeks (min-max: 30–40), and the median neonatal birth weight was 3160 g (min-max: 1300–4424). The median Apgar scores were 8 (min-max: 2–10) at 1 min and 9 (min-max: 7–10) at 5 min. Vaginal delivery occurred in 314 patients (78.5%). No significant differences were observed in first-trimester Hb, Hct, or ferritin levels with respect to combined neonatal outcomes (p=0.281, 0.369, and 0.905, respectively).

The correlation between first-trimester ferritin levels and maternal characteristics was evaluated. A significant positive correlation was observed between first-trimester ferritin and BMI, postpartum Hb and Hct, and 1 and 5 min APGAR scores. A significant negative correlation was observed between first-trimester ferritin and parity (Table 2).

Comparison of first-trimester Hb, Hct, and ferritin levels according to postpartum transfusion status revealed significant differences for all three parameters (p<0.001, <0.001, and 0.012, respectively) (Table 3). The optimal first-trimester cut-off values for predicting postpartum transfusion

Table 1. Comparison of demographic characteristics according to postpartum transfusion status

Variable	No transfusion median (Min-Max)	Transfusion median (Min-Max)	*p*
Age (years)	28 (19–42)	32 (22–40)	**0.019**
Body mass index (kg/m^2)	25 (17–47)	25 (21–35)	0.968
Parity	1 (0–4)	2 (0–5)	**<0.001**

Table 2. Correlation between first-trimester ferritin levels and maternal-neonatal parameters

	Spearman's r	*p*
Maternal outcomes		
Maternal age	–0.049	0.333
BMI (kg/m^2)	+0.159	**0.001**
Parity	–0.102	**0.041**
Gestational age at delivery	—	0.510
Postpartum hemoglobin	+0.126	**0.011**
Postpartum hematocrit	+0.115	**0.022**
Fetal/Neonatal outcomes		
1st-min APGAR score	+0.143	**0.004**
5th-min APGAR score	+0.103	**0.039**
Neonatal birth weight	—	0.956
Neonatal hemoglobin	—	0.069
Neonatal hematocrit	—	0.070

BMI: Body mass index, Hb: Hemoglobin, Hct: Hematocrit, APGAR: Appearance, Pulse, Grimace, Activity, Respiration

Table 3. Predictive performance of first-trimester parameters for postpartum transfusion

Variable	Cut-off	Sensitivity (%)	Specificity (%)	AUC	95% CI	*p*
Hemoglobin (g/dL)	12.05	70	69	0.750	0.65–0.84	<0.001
Hematocrit (%)	36.05	70	66	0.745	0.64–0.84	<0.001
Ferritin (µg/L)	19.60	60	63	0.634	0.54–0.71	0.012

*Cut-off values were determined according to the Youden index. AUC: Area under the curve, CI: Confidence interval.

Table 4. Logistic regression analysis of factors associated with postpartum transfusion

Variable	B	S.E.	Wald	*p*	OR	95% CI
First-trimester ferritin	−0.025	0.013	3.654	0.056	0.975	0.950–1.001
Parity	+0.615	0.181	11.575	**0.001**	1.849	1.298–2.635
Age	—	—	—	—	—	—

OR: Odds ratio, CI: Confidence interval, S.E.: Standard error, B: Regression coefficient.

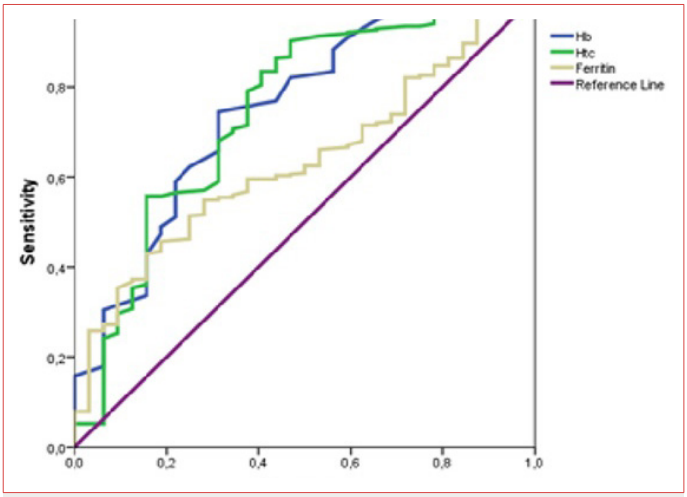

Figure 1. Receiver operating characteristic (ROC) curves of first-trimester hemoglobin (Hb), hematocrit (Hct), and ferritin levels for predicting postpartum transfusion.

were 12.05 g/dL for Hb (70% sensitivity, 69% specificity), 36.05% for Hct (70% sensitivity, 66% specificity), and 19.6 µg/L for ferritin (60% sensitivity, 63% specificity) (Fig. 1).

In the multivariable logistic regression model including parity, age, and first-trimester ferritin; parity remained an independent predictor of postpartum transfusion (Odds ratio [OR]=1.85, *p*=0.001). First-trimester ferritin level demonstrated a borderline inverse association with transfusion risk (OR=0.98, p=0.056) in the model, suggesting that lower iron stores may predispose to transfusion when unadjusted for Hb. Maternal age was not a significant factor (Table 4).

DISCUSSION

The most important finding of our study is the identification of a first-trimester ferritin cut-off of 19.6 µg/L that predicts the need for postpartum transfusion in non-anemic patients. To the best of our knowledge, no prior study has established a ferritin threshold specifically for this outcome, making our results a novel contribution to maternal hematology and patient blood management (PBM).

International literature strongly supports the role of ferritin as the most robust early pregnancy biomarker for later hematologic outcomes.[11] Judistiani *et al.*[12] demonstrated that first-trimester ferritin ≤27.3 µg/L was the best predictor of third-trimester anemia. In this study, a cut-off value for ferritin was determined; however, only Hb levels in the last trimester were assessed, and postpartum follow-up was not conducted. Similarly, Resseguier *et al.*,[13] in a French cohort, found that first-trimester Hb and ferritin were reliable predictors of third-trimester anemia, though their study did not extend the outcome to transfusion. It can be anticipated that iron stores will predict subsequent anemia; however, it should be noted that the early postpartum period, referred to as the fourth stage of labor, is also part of pregnancy follow-up. The fact that this period constitutes the endpoint of our study distinguishes it from others.

Similar to our study, Crispin *et al.*[11] showed that ferritin measured in the first trimester, but not later in pregnancy, was predictive of anemia at delivery and suggested ferritin screening as part of patient PBM programs. These findings align with ours, but our study extends the predictive value of ferritin from anemia to the more clinically tangible outcome of transfusion, thereby filling a critical gap.

Another key consideration is the threshold used to define iron deficiency. WHO recommends <15 µg/L, while most guidelines adopt <30 µg/L, based on bone marrow iron depletion.[7,8] Recently, Mei *et al*.[14] analyzed 1040 pregnant women's NHANES data and proposed physiologically based trimester-specific thresholds: ~25 µg/L for the first trimester. Moreover, it was reported that the value identified in this study was not influenced by ethnic differences. These thresholds, which better align with iron physiology, indicate that the prevalence of iron deficiency in pregnancy has likely been underestimated when the traditional 15 µg/L cut-off is applied. In our study, however, the median value was found to be 22.65 µg/L. The clinical relevance of these findings is substantial. Anemia is a well-documented risk factor for adverse peripartum outcomes, including postpartum hemorrhage, transfusion, and maternal morbidity.

Our study demonstrated that when a ferritin cut-off value of 30 µg/L was applied, two-thirds (66.6%) of women in the first trimester were identified as having depleted iron stores, whereas using a threshold of 15 µg/L classified 116 patients (29%) as such. In contrast, applying our ferritin and Hb thresholds clearly identifies a much sensible proportion in non-anemic patients. This finding highlights the insufficiency of screening approaches based solely on hemogram parameters. By integrating ferritin into routine first-trimester antenatal screening, as already suggested by national guidelines in some countries, earlier detection and intervention could significantly reduce both third-trimester anemia and postpartum transfusion rates.[10,15]

From a health policy perspective, these results also contribute to patient blood management strategies. Early treatment of iron deficiency is cost-effective, reduces transfusion demand, and improves maternal outcomes. Systematic ferritin screening in the first trimester, combined with individualized treatment thresholds, may be a more efficient strategy than universal supplementation or reliance on Hb alone.

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings. Second, factors such as dietary intake, inflammatory status, or chronic subclinical infections that could influence ferritin levels were not systematically evaluated. Third, although postpartum transfusion was selected as a clinically objective endpoint, longer-term follow-up – including postpartum iron status and recovery – was not available. Finally, despite these limitations, the large sample size and uniform data collection strengthen the reliability of our results. As a conclusion, our study demonstrates that first-trimester ferritin serves as a novel predictor of postpartum transfusion.

CONCLUSION

The cut-off of 19 µg/L we identified provides a population-specific threshold with immediate clinical and public health relevance. These findings emphasize the importance of including ferritin in routine first-trimester screening, refining PBM protocols, and guiding early iron supplementation strategies. Future multicenter validation studies are warranted to confirm these results and assess their generalizability across diverse populations.

DECLARATIONS

Ethics Committee Approval: Ethical approval for this study was obtained from the Lokman Hekim University Scientific Research Ethics Committee (Date: 28.03.2024, Approval No: 2024/89).

Informed Consent: Written informed consent was obtained.

Conflict of Interest: None declared.

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Evaluation of the Effect of Weight Loss After Sleeve Gastrectomy on Ventricular Repolarization Parameters

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ABSTRACT

Objective: Obesity is associated with adverse alterations in ventricular repolarization and increased electrophysiological heterogeneity. Sleeve gastrectomy provides substantial and sustained weight loss; however, its effects on ventricular repolarization parameters assessed by surface electrocardiography (ECG) remain incompletely characterized. The aim of this study was to evaluate the effect of weight loss after sleeve gastrectomy on ventricular repolarization parameters assessed by surface ECG.

Materials and Methods: This retrospective study included 95 morbidly obese patients who underwent laparoscopic sleeve gastrectomy. Standard 12-lead electrocardiograms were evaluated preoperatively and during routine follow-up approximately 6 months after surgery. Changes in ventricular repolarization parameters were analyzed in relation to post-operative weight loss.

Results: Substantial weight loss was observed at follow-up. Among time-based electrocardiographic parameters, modest but statistically significant post-operative reductions were detected in corrected QT interval (QTc), QT interval dispersion (QTd), and corrected JT interval (JTc), while all values remained within generally accepted physiological ranges. In addition, ratio-based indices reflecting relative depolarization-repolarization timing, including Tpeak–Tend dispersion/QT and QRS duration/QT, showed significant post-operative decreases. No significant post-operative changes were observed in other ventricular repolarization parameters.

Conclusion: Weight loss following sleeve gastrectomy was associated with subtle changes in selected ventricular repolarization parameters detectable on surface ECG, suggesting limited electrophysiological adaptation rather than overt alterations in myocardial conduction or repolarization. The clinical implications of these findings remain uncertain, and further prospective studies with longer follow-up are warranted to clarify the electrophysiological effects of sleeve gastrectomy.

Keywords: JTc interval, Obesity, QT dispersion, QTc interval, Sleeve gastrectomy, Ventricular repolarization

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INTRODUCTION

Obesity is a preventable metabolic risk factor that is rapidly increasing globally and is considered a significant public health problem.[1] Excess body weight is associated not only with metabolic disorders but also with an increased risk of coronary heart disease and sudden cardiac death.[2-4] Furthermore, obesity has been shown to adversely affect cardiac electrical stability, with evidence of altered ventricular repolarization and increased electrophysiological heterogeneity. These changes are thought to arise in part from obesity-related myocardial remodeling and ectopic adipose tissue accumulation, ultimately leading to complex alterations in cardiac structure and electrical conduction.[2,5,6] Moreover, a better understanding of obesity-related electrocardiographic changes and the identification of cardiac risk markers reflecting these processes is becoming increasingly important.

In terms of effective and sustainable weight loss, long-term studies have shown that diet and lifestyle interventions generally result in modest weight loss, while pharmacological treatments provide a slightly greater but still limited effect over time.[7] Therefore, it is stated that achieving permanent weight loss is often only possible with surgical methods, especially in individuals resistant to lifestyle and medical approaches.[7-10] Bariatric surgery stands out as a powerful treatment option because it provides significant and long-term weight loss, as well as reducing cardiometabolic morbidity, and long-term mortality.[8,10] According to the international records, sleeve gastrectomy is the most commonly performed bariatric procedure worldwide.[11] With the demonstration of the beneficial effects of weight loss on cardiac functions, studies examining changes in parameters reflecting ventricular repolarization on electrocardiography (ECG) before and after obesity surgery have also increased in recent years.[12-14]

It has been reported that obese individuals show significant impairments in ECG parameters reflecting the duration and homogeneity of ventricular repolarization.[15] Significant and sustained weight loss achieved after bariatric surgery has been shown to reduce repolarization heterogeneity by significantly decreasing corrected QT dispersion (QTcd), corrected JT dispersion (JTcd), and transmural repolarization indicators.[13] In addition, the ameliorative effects of weight loss on corrected QT interval (QTc) and QTcd have been reported, particularly in relation to the regression of left ventricular hypertrophy.[14] Sleeve gastrectomy series also report that, consistent with these findings, significant improvements can be observed in parameters related to ventricular repolarization measured on ECG in the post-operative period, and this may potentially contribute to a reduction in the risk of ventricular arrhythmias and sudden cardiac death; however, it has been emphasized that these results need to be confirmed in larger cohorts.[12]

Therefore, it is clear that further studies are needed to better understand the changes in electrocardiographic parameters associated with ventricular repolarization after sleeve gastrectomy. The aim of this study is to evaluate the effect of post-operative weight loss on ventricular repolarization indices in morbidly obese patients who underwent sleeve gastrectomy.

MATERIALS AND METHODS

The study was approved by the Gaziantep University Clinical Research Ethics Committee (Decision No: 2023/244, Date: 29.08.2023). We retrospectively included a total of 95 patients who underwent laparoscopic sleeve gastrectomy at the Gaziantep University General Surgery Clinic between January 2018 and January 2023. The study was conducted in accordance with the Declaration of Helsinki. Demographic and clinical data – including age, sex, body mass index (BMI), pre-operative and 6-month post-operative weight, comorbidities, smoking status, and American Society of Anesthesiologists (ASA) classification – were routinely recorded during anesthesia preparation. The necessary information was retrieved from the hospital's electronic medical record system and, when required, from archived paper files.

Patients with BMI ≥40 kg/m^2, or ≥35 kg/m^2 accompanied by obesity-related comorbidities who failed to achieve adequate weight loss with conservative methods, were considered eligible for surgery. Because this study was retrospective and pre-operative echocardiography is not routinely performed during the standard pre-operative anesthesia evaluation in our center, echocardiographic data were not available for all patients. However, if a previous echocardiogram in the patient record showed structural abnormalities – such as left-ventricular systolic dysfunction (Ejection fraction <50%), significant valvular disease, or left ventricular hypertrophy – these patients were excluded to avoid confounding effects on ventricular repolarization. Additional exclusion criteria included ischemic heart disease, electrolyte imbalance, Type 1 diabetes, missing ECG data, and the use of medications known to affect cardiac conduction. Stable, well-controlled hypertension was included, whereas patients with chronically uncontrolled hypertension or documented end-organ involvement were excluded from the study.

All operations were performed laparoscopically under general anesthesia. A 38–40 Fr bougie was used for sleeve calibration, and gastric resection was initiated 2–10 cm proximal to the pylorus.

Pre-operative ECGs were obtained during routine anesthesia preparation, while post-operative ECGs were retrieved from routine follow-up visits performed approximately 6 months after surgery. All ECGs were digitally magnified and analyzed using imaging software (Adobe Photoshop, Version 19.1.6). Two cardiologists, who were unaware of any clinical information, independently assessed each ECG recording. If there were differences in measurements, the final value was calculated as the average of the two measurements to reduce variability between observers.

The study analyzed the following ECG parameters:

QRS duration (QRSd), QT, JT interval (JT), and Tpeak–Tend interval (Tp–e) were measured on standard 12-lead ECGs following established definitions. QRSd was measured from the start to the end of the QRS complex in each lead. The QT was measured from the start of the QRS complex to the end of the T wave, where it returned to the baseline. The JT was derived by subtracting QRSd from the QT (JT = QT - QRSd). The Tp–e was defined as the time from the peak of the T wave to its end.

To evaluate spatial variations in ventricular activation and recovery, dispersion values were calculated across all 12 leads. QRS dispersion, QT dispersion (QTd), JT dispersion (JTd), and Tp–e dispersion (Tp–ed) were defined as the difference between the highest and lowest values recorded across the leads.

To reduce the effect of heart rate on interval readings, corrected indices were calculated. QTc and corrected JT (JTc) values were computed using Bazett's formula.[16]

Ratio-based parameters, including Tp–e/QT, Tp-e/QRSd, and QRSd/QT, were determined from the respective interval readings.

To measure changes after surgery, delta (Δ) values were computed for each parameter using the formula Δ = pre-operative measurement – post-operative measurement. Positive Δ values indicated a decrease after surgery, while negative values showed an increase.

All time intervals were reported in milliseconds (ms). To avoid confusion with QRSd, the term QRS dispersion was always written out fully in the manuscript.

Statistical Analysis

The Shapiro–Wilk test was used to determine whether numerical data had a normal distribution. Two dependent measurements of normally distributed variables were compared using a paired t-test, whereas two dependent measurements of non-normally distributed variables were compared using a Wilcoxon test. The Chi-square test was used to examine relationships between categorical variables. Correlation coefficients were calculated to assess relationships between numerical variables.

These Δ values were compared between groups using the Mann–Whitney U test.

All analyses were performed using the Statistical Package for Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA). A $p<0.05$ was considered statistically significant.

RESULTS

A total of 95 patients who underwent laparoscopic sleeve gastrectomy were evaluated in the study. Of these, 24 (25.3%) were male, and 71 (74.7%) were female. Among the study population, hypertension was present in 11 patients (11.6%), diabetes mellitus in 15 (15.8%), thyroid disease in 12 (12.6%), asthma in 9 (9.5%), insulin resistance in 6 (6.3%), and obstructive sleep apnea syndrome in 3 (3.2%). Thirty-two patients (33.7%) were active smokers. According to the ASA classification, 26 patients (27.4%) were classified as ASA II, while 69 (72.6%) were ASA III (Table 1).

The average age of participants was 35.47±11.71 years, with an age range of 18–64 years. The mean pre-operative BMI was 45.82±6.52 kg/m^2, while the mean BMI at 6 months postoperatively was 33.29±4.66 kg/m^2. Similarly, the mean pre-operative body weight was 125.82±19.43 kg, which decreased to 91.43±13.58 kg at 6 months following surgery.

Table 1. Baseline demographic and clinical characteristics of the patients (*n*=95)

Variable	*n*	Percentage
Male	24	25.3
Female	71	74.7
Hypertension	11	11.6
Diabetes mellitus	15	15.8
Obstructive sleep apnea syndrome	3	3.2
Thyroid disease	12	12.6
Asthma	9	9.5
Insulin resistance	6	6.3
Smoker	32	33.7
ASA physical status II	26	27.4
ASA physical status III	69	72.6

n: Number of patients, DM: Diabetes mellitus, OSAS: Obstructive sleep apnea syndrome, ASA: American Society of Anesthesiologists

Table 2. Mean values of demographic and anthropometric measurements (*n*=95)

Variable	Mean±SD	Median (Min-Max)
Age (years)	35.47±11.71	34 (18–64)
BMI (baseline) (kg/m^2)	45.82±6.52	44.3 (36.8–66)
BMI (6 months after surgery) (kg/m^2)	33.29±4.66	32.2 (24.8–47.4)
Weight (baseline) (kg)	125.82±19.43	120 (91–184)
Weight (6 months after surgery) (kg)	91.43±13.58	90 (64–130)
Amount of weight loss (kg)	34.39±7.30	33 (19–60)

n: Number of patients, BMI: Body mass index, SD: Standard deviation, Min-Max: Minimum-maximum, kg: Kilogram, kg/m^2: Kilogram/square meter

The mean total weight loss at the end of the 6-month follow-up period was 34.39±7.30 kg. The median values and ranges for each parameter are presented in Table 2.

Comparisons between baseline and post-operative 6-month electrocardiographic parameters are presented in Table 3. QTc values showed a significant decrease from 418.45±28.25 ms preoperatively to 412.01±28.27 ms postoperatively (p=0.013). QTd was also modest but statistically significantly reduced at the 6th post-operative month (53.93±10.95 ms vs. 52.57±10.20 ms, p=0.041). JTc values were significantly lower at follow-up compared with baseline (330.33±28.38 ms vs. 323.62±28.84 ms, p=0.017).

Table 3. Comparisons of baseline and post-operative 6th-month ECG findings

Parameter	Pre-operative (Mean±SD)	Post-operative (Mean±SD)	*p*
QTc	418.45±28.25	412.01±28.27	**0.013***
QTd	53.93±10.95	52.57±10.20	**0.041***
Tp-e	87.31±8.13	87.15±8.98	0.598
Tp-ed	55.98±15.49	57.43±17.02	0.722
Tp-e/QT	0.25±0.05	0.24±0.03	**0.011***
JTc	330.33±28.38	323.62±28.84	**0.017***
JTd	38.87±6.19	38.55±7.09	0.244
QRSd	88.13±8.81	88.39±7.62	0.836
QRS dispersion	28.12±3.52	28.38±3.95	0.549
QRSd/QT	0.25±0.03	0.24±0.03	**0.008***
Tp-e/QRSd	1.00±0.13	0.99±0.12	0.864

**p*: Statistical significance (*p*<0.05, Wilcoxon signed-rank test). All time-based ECG measurements were recorded in milliseconds. QTc: Corrected QT interval, QTd: QT dispersion, QT: QT interval, JTc: Corrected JT interval, JTd: JT dispersion, Tp–e: Tpeak–Tend interval, Tp–ed: Tpeak–Tend dispersion, QRSd: QRS duration, QRS dispersion: Maximum-minimum QRS duration across 12 leads, SD: Standard deviation

Although the absolute reductions observed in QTc, QTd, and JTc were modest in magnitude and both pre-operative and post-operative values remained within generally accepted normal ranges, these changes may reflect a subtle improvement in global ventricular repolarization timing and should be interpreted as surrogate electrophysiological markers rather than direct indicators of clinical risk reduction.

Regarding ratio-based parameters, the Tp–e/QT ratio demonstrated a small but statistically significant post-operative reduction (0.25±0.05 vs. 0.24±0.03, p=0.011). Similarly, the QRSd/QT ratio showed a modest yet statistically significant decrease at 6 months after surgery (0.25±0.03 vs. 0.24±0.03, p=0.008).

In contrast, no statistically significant differences were detected in Tp–e, Tp–ed, JTd, QRSd, QRS dispersion, or Tp–e/QRSd values (all p>0.05).

Comparative Δ (delta) values for female and male patients are shown in Table 4. No statistically significant variation was detected between the groups across any of the evaluated parameters (p>0.05).

Post-operative changes expressed as Δ values differed according to smoking status (Table 5). While no significant differences were observed between smokers and non-smokers for ΔBMI, ΔQTc, ΔTp–e, ΔTp–e/QT, ΔJTc, ΔJTd, ΔQRSd, QRSd/QT, or ΔTp–e/QRSd (all p>0.05), dispersion-based parameters demonstrated significant between-group differences. Specifically, ΔTp–ed was significantly different between smokers and non-smokers (–3.59±12.38 vs. 2.75±9.43, p=0.036), indicating a post-operative reduction in smokers and a relative post-operative increase in non-smokers (Fig. 1). Similarly, ΔQRS dispersion was significantly lower in smokers compared with non-smokers (–0.89±3.87 vs. 0.97±3.51, p=0.031), reflecting a post-operative decrease among smokers, whereas non-smokers exhibited a relative post-operative increase (Fig. 2). In addition, ΔQTd showed a borderline difference between smokers and non-smokers (p=0.059), indicating a trend toward a greater post-operative reduction in smokers that did not reach conventional statistical significance.

DISCUSSION

Obesity is known to alter the myocardial electrical environment through several mechanisms, including left ventricular hypertrophy, increased sympathetic activity, inflammation, oxidative stress, and excess pericardial and myocardial fat accumulation.[6] These alterations contribute to

Table 4. Comparison of Δ values (pre-operative – post-operative) according to gender

Parameter	Female (Mean±SD)	Median (Q1–Q3)	Male (Mean±SD)	Median (Q1–Q3)	*p*
ΔBMI	12.5±2.34	12.2 (10.8–13.6)	12.55±2.69	12.73 (10.8–13.3)	0.905
ΔQTc	4.8±40.59	8 (–14–28)	11.29±21.47	6.5 (–7.5–26)	0.451
ΔQTd	1.2±7.44	4 (–4–6)	1.83±7.42	2.5 (–4–6)	0.976
ΔTp-e	0.1±8.83	–2 (–4–4)	0.33±11.12	2 (–4–4)	0.782
ΔTp-ed	–1.58±12.47	2 (–6–6)	–1.08±9.83	2 (–7–5)	0.993
ΔTp-e/QT	0.02±0.06	0.01 (–0.02–0.03)	0.01±0.04	0.01 (–0.01–0.03)	0.784
ΔJTc	5.30±39.14	4.0 (–10.5–24.0)	10.88±22.84	9.5 (–9.25–26.75)	0.443
ΔJTd	0.14±5.79	2 (–4–4)	0.88±5.27	2 (–3.5–4)	0.983
ΔQRSd	–0.49±8.08	0 (–4–4)	0.42±7.64	1 (–4–4)	0.717
ΔQRS dispersion	–0.58±3.90	–2 (–4–2)	0.67±3.56	2 (–2–2)	0.203
ΔQRSd/QT	0.01±0.03	0.01 (–0.01–0.03)	0.01±0.03	0.01 (–0.01–0.03)	0.962
ΔTp-e/QRSd	0.01±0.11	0 (–0.06–0.05)	0.01±0.11	0.01 (–0.03–0.05)	0.613

**p*: statistical significance ($p<0.05$, Mann–Whitney U test); Δ was calculated as pre-operative value – post-operative value. Positive Δ indicates a decrease in post-operative values, whereas negative Δ indicates an increase. All time-based ECG measurements were recorded in milliseconds. BMI: Body mass index, QTc: corrected QT interval, QTd: QT dispersion, QT: QT interval, JTc: Corrected JT interval, JTd: JT dispersion, Tp–e: Tpeak–Tend interval, Tp–ed: Tpeak–Tend dispersion, QRSd: QRS duration, QRS dispersion: Maximum-minimum QRS duration across 12 leads, SD: Standard deviation, Q1-Q3: Interquartile range.

Table 5. Comparison of Δ values (Pre-operative – Post-operative) according to smoking status

Parameter	Non-smoker (Mean±SD)	Median (Q1–Q3)	Smoker (Mean±SD)	Median (Q1–Q3)	*p*
ΔBMI	12.54±2.56	12.2 (10.8–13.6)	12.46±2.16	12.5 (10.65–13.55)	0.887
ΔQTc	5.79±42.21	9 (–14–30)	7.72±22.81	3 (–10–24.5)	0.922
ΔQTd	0.21±7.33	2 (-4–6)	3.63±7.11	4 (–2–8)	0.059
ΔTp-e	0.03±9.77	–2 (–4–4)	0.41±8.77	2 (–4–4)	0.994
ΔTp-ed	–3.59±12.38	0 (–8–4)	2.75±9.43	3 (–4–7)	**0.036***
ΔTp-e/QT	0.02±0.07	0 (–0.02–0.03)	0.02±0.03	0.01 (–0.01–0.03)	0.254
ΔJTc	6.29±41.5	4.0 (–11.5–26.5)	7.53±20.5	5.5 (–9.3–22.0)	0.375
ΔJTd	0±6.2	2 (–4–4)	0.97±4.37	2 (–2–4)	0.398
ΔQRSd	–0.49±7.88	–1 (–4–2)	0.19±8.17	2 (–4–4)	0.246
ΔQRS dispersion	–0.89±3.87	–2 (–3–2)	0.97±3.51	2 (–2.5–3.5)	**0.031***
QRSd/QT	0.01±0.03	0.01 (–0.01–0.02)	0.01±0.02	0.01 (–0.01–0.03)	0.274
ΔTp-e/QRSd	0.01±0.11	0.01 (–0.06–0.05)	0.01±0.11	0 (–0.04–0.04)	0.856

**p*: Statistical significance ($p<0.05$, Mann–Whitney U test); Δ was calculated as pre-operative value – post-operative value. Positive Δ indicates a decrease in post-operative values, whereas negative Δ indicates an increase. All time-based ECG measurements were recorded in milliseconds. BMI: Body mass index, QTc: Corrected QT interval, QTd: QT dispersion, QT: QT interval, JTc: Corrected JT interval, JTd: JT dispersion, Tp–e: Tpeak–Tend interval, Tp–ed: Tpeak–Tend dispersion, QRSd: QRS duration, QRS dispersion: Maximum-minimum QRS duration across 12 leads, SD: Standard deviation, Q1-Q3: Interquartile range.

adverse structural and electrophysiological remodeling and to the development of obesity-associated cardiomyopathy.[6] Prolonged and heterogeneous ventricular repolarization is a characteristic feature of obesity-related electrical abnormalities.[14] Accordingly, obesity-related myocardial changes have been clinically associated with delayed ventricular repolarization and increased repolarization dispersion on surface ECG.[15] Within this context, the present study examined post-operative changes in ventricular repolarization parameters following sleeve gastrectomy.

QTc is widely used as a heart rate-corrected measure of overall ventricular repolarization duration, whereas

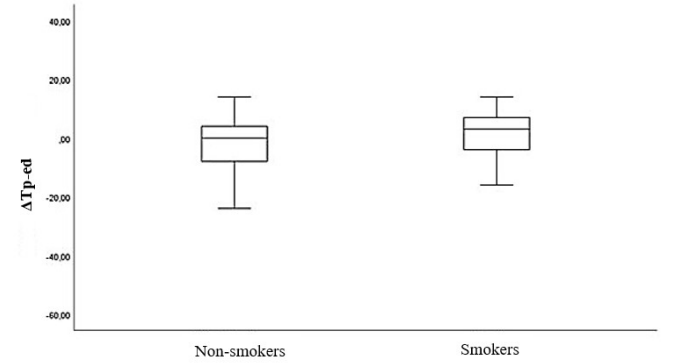

Figure 1. Comparison of ΔTp–ed values between smokers and non-smokers. Box-and-whisker plots illustrate the distribution of ΔTp–ed values by smoking status. Δ values were defined as the difference between pre-operative and post-operative measurements. Negative Δ values reflect an increase in post-operative Tp–ed, whereas positive Δ values indicate a post-operative reduction. A significant between-group difference was observed, with smokers showing a post-operative decrease in Tp–ed and non-smokers demonstrating a relative post-operative increase (p=0.036, Mann-Whitney U test). Tp–ed: Tpeak–Tend dispersion, Δ: Pre-operative minus post-operative.

Figure 2. Comparison of ΔQRS dispersion values between smokers and non-smokers. Box-and-whisker plots illustrate the distribution of ΔQRS dispersion values by smoking status. Δ values were defined as the difference between pre-operative and post-operative measurements. Negative Δ values reflect an increase in post-operative QRS dispersion, whereas positive Δ values indicate a post-operative reduction. A significant between-group difference was observed, with smokers showing a post-operative decrease in QRS dispersion and non-smokers demonstrating a relative post-operative increase (p=0.031, Mann-Whitney U test). QRS dispersion: Interlead dispersion of QRS duration, Δ: Pre-operative minus post-operative.

QTd was proposed as an electrocardiographic index reflecting interlead variability and spatial heterogeneity of ventricular repolarization.[17] However, QTc and QTd have been controversially affected across studies. According to the results of a study conducted by Alam et al.,[18] in 11 patients who underwent gastric banding or biliopancreatic diversion, QTc values showed no significant change despite weight loss during the 12-month post-operative follow-up. Similarly, Doherty et al.[19] compared the diet group with the control group in their study of 20 women who lost weight through dieting, but no significant change in QTc values was observed. Gupta et al.[20] demonstrated that weight loss achieved with a low-calorie liquid protein diet was associated with changes in QTd in obese patients. Al-Salameh et al.[21] found that 28 patients who had sleeve gastrectomy had significantly lower mean QTc values. However, there was no link discovered between QTc alteration and weight loss. Russo et al.[13] performed jejunoileal bypass on 100 obese patients, and QTc and QTcd values of the patients decreased significantly 1 year postoperatively. In a recent study by Gul et al.,[12] a non-significant increase in the QTc interval was observed in 48 patients who underwent sleeve gastrectomy, while a statistically significant decrease in QTcd was noted. In this study, patients were evaluated at 1 and 6 months after sleeve gastrectomy. In the present study, QTc values showed a modest but statistically significant reduction at 6 months after sleeve gastrectomy; however, mean QTc values remained within the generally accepted normal range both preoperatively and postoperatively (418.45±28.25 ms vs. 412.01±28.27 ms). This change was accompanied by a significant decrease in QTd, which also remained within physiological limits (53.93±10.95 ms vs. 52.57±10.20 ms). These findings indicate that weight loss achieved after sleeve gastrectomy shifts ventricular repolarization toward a shorter and more homogeneous timing pattern while remaining within accepted normal limits.

Both QTcd and JTcd serve as indicators of localized differences in ventricular recovery time and myocardial action potential duration.[13] Compared with QT-based indices, JT-related parameters have been proposed as more specific markers of ventricular repolarization, particularly when depolarization duration may influence QT measurements.[22] In the study by Russo et al.,[13] which included severely obese patients undergoing bariatric surgery, JTc values were reported to decrease significantly at 12 months postoperatively. Similarly, in the study by Gul et al.,[12] both JTc and JTcd showed significant reductions following bariatric surgery, suggesting a more homogeneous ventricular repolarization profile after sustained weight loss. In our cohort, JTc demonstrated a modest but statistically significant reduction at 6 months after

sleeve gastrectomy, whereas JTd remained unchanged. This dissociation between changes in JTc and JTd may reflect earlier functional adaptation of global repolarization timing compared with indices reflecting spatial heterogeneity of ventricular repolarization, which may require longer follow-up to show measurable change.

QRSd reflects the temporal characteristics of ventricular depolarization on surface ECG.[23] In the overall study population, no significant change was observed in QRSd or QRS dispersion at 6 months after sleeve gastrectomy, whereas a modest decrease, but statistically significant in the QRSd/QT ratio was noted. This finding should be interpreted in conjunction with other electrocardiographic parameters, as ratio-based indices may reflect combined changes in depolarization and repolarization rather than isolated conduction alterations.

The Tp–e has been defined as an electrocardiographic parameter reflecting the terminal phase of ventricular repolarization and has been proposed as an index of transmural dispersion of myocardial repolarization.[24] In contrast, clinical surface electrocardiographic measurements suggest that the Tp–e may represent a more global feature of repolarization dispersion rather than a direct measure of transmural heterogeneity, and therefore should be interpreted as a surrogate electrophysiological marker.[25]

In this context, Inanır et al.[26] demonstrated that Tp–e and Tp–e/QTc were significantly prolonged in individuals with extreme obesity compared with healthy controls, suggesting an association between obesity and altered ventricular repolarization characteristics. Similarly, Gul et al.[12] reported significant reductions in Tp–e, Tp–e/QT, and Tp–e/QTc following marked weight loss after bariatric surgery, indicating favorable modulation of repolarization-related indices.

In our study, although no significant change was observed in absolute Tp–e or Tp–ed at 6 months after sleeve gastrectomy, a statistically significant reduction was detected in the Tp–e/QT ratio. This finding suggests that early post-operative electrophysiological adaptations may be more readily captured by ratio-based indices than by absolute time-based or dispersion measures. Consistent with this interpretation, Smetana et al.[27] emphasized that Tp–e measurements derived from surface ECG are influenced by interindividual anatomical and electrical variability and may therefore exhibit considerable person-to-person variation in clinical populations. By normalizing repolarization dispersion to overall repolarization time, the Tp–e/QT ratio may allow a more consistent assessment of repolarization dynamics on surface ECG.[28]

In our study, no significant differences were observed between genders in terms of weight loss or ventricular repolarization parameters at baseline or at 6 months postoperatively. Although the study population was predominantly female, this distribution is consistent with previous reports in bariatric surgery and weight-loss studies.[15,22]

Accumulating evidence indicates that smoking adversely affects myocardial electrical properties through mechanisms such as oxidative stress, inflammation, endothelial dysfunction, and fibrotic remodeling,[29,30] thereby contributing to increased regional heterogeneity of ventricular depolarization and repolarization. Despite these well-recognized adverse effects, the present study demonstrated a relatively greater reduction in Tp–ed (Fig. 1) and QRS dispersion (Fig. 2) among smokers than non-smokers after sleeve gastrectomy. In addition, ΔQTd showed a borderline between-group difference (p=0.059), suggesting that smoking status may exert a more pronounced influence on dispersion-based repolarization parameters, although this finding did not reach conventional statistical significance. This finding may suggest that smoking-related electrophysiological disturbances of the myocardium could regress more rapidly in the context of substantial weight loss. In addition, within our routine clinical practice, patients are strongly advised to quit smoking – particularly during the early post-operative period in conjunction with lifestyle and nutritional optimization – which may have resulted in reduced post-operative exposure to cigarette smoke. Such a reduction could theoretically contribute to autonomic and electrophysiological adaptation processes, thereby influencing post-operative ventricular repolarization parameters. Accordingly, smoking status should be considered not as a constant variable during the post-operative period but rather as a behavioral factor that may change over time. Importantly, evaluating changes in ventricular repolarization parameters according to smoking status was not among the primary aims of this study. Moreover, the number of patients within the smoking subgroups was relatively limited, and the study was not specifically powered to draw definitive conclusions based on smoking status alone, which further warrants a cautious interpretation of these findings. Nevertheless, when the overall pattern emerging from the analysis is considered, smoking status should be regarded as a potential confounding factor that may influence post-operative ventricular repolarization dynamics. Therefore, the changes observed in dispersion-based indices among smokers after weight loss should not be interpreted as definitive indicators of restored electrical homogeneity.

In summary, this study demonstrated that weight loss achieved after sleeve gastrectomy was associated with modest

but statistically significant changes in certain ventricular repolarization parameters assessed by surface ECG. These changes occurred while all measured parameters remained within accepted physiological ranges and therefore appear to reflect subtle electrophysiological adaptations observed on surface ECG rather than overt abnormalities in ventricular conduction or repolarization. In particular, changes observed in ratio- and dispersion-based indices that jointly evaluate depolarization-repolarization timing may indicate a limited but measurable reorganization of myocardial electrical properties following substantial weight loss. Nevertheless, because these findings are derived from surface ECG measurements, interpretation of their clinical implications should be made with caution. Further prospective studies incorporating long-term follow-up and comprehensive assessments are needed to better clarify the electrophysiological changes observed after bariatric surgery.

Limitations

This study was conducted at a single tertiary center with a retrospective design, which may limit external generalizability. In addition, the 6-month follow-up period was relatively short to capture long-term electrophysiological remodeling or clinically relevant arrhythmic outcomes, and therefore, the findings should be interpreted as early post-operative adaptations rather than definitive long-term effects. Moreover, post-operative ECGs were obtained during routine follow-up visits, and not all patients were evaluated at an identical time point; minor variability around the 6-month assessment may have occurred, which could have influenced the magnitude of observed electrophysiological changes.

In addition, no data on clinical arrhythmic events or sudden cardiac death were available; therefore, all interpretations are restricted to electrocardiographic surrogate markers rather than clinical arrhythmic outcomes.

Autonomic nervous system activity was not directly assessed, and biochemical variables such as electrolyte balance, hormonal status, and inflammatory markers were not incorporated into the analysis, all of which may influence ventricular repolarization indices. Moreover, routine pre-operative echocardiography was not available for all patients due to the retrospective nature of the study. Although patients with documented structural heart disease or left ventricular hypertrophy were excluded when prior echocardiographic data were available, subclinical structural alterations cannot be completely ruled out and may have influenced surface ECG findings.

Electrocardiographic parameters were measured manually, which may introduce observer-related variability despite careful standardization. Although all measurements were independently performed by two blinded cardiologists and final values were obtained by averaging the measurements, formal interobserver reliability statistics, such as intraclass correlation coefficients, were not calculated.

The absence of a non-surgical or normal-weight control group precludes causal inference regarding the extent to which the observed electrophysiological changes can be attributed solely to weight loss, independent of other perioperative or lifestyle-related factors. In addition, post-operative behavioral variables, including changes in smoking habits, physical activity, and dietary adherence, were not prospectively quantified and may have acted as confounding factors influencing ventricular repolarization dynamics.

Future multicenter prospective studies with larger sample sizes, longer follow-up durations, standardized electrophysiological assessments, and multivariate models incorporating lifestyle, metabolic, autonomic, and imaging-based parameters are warranted to validate and extend these findings.

CONCLUSION

In this study, substantial weight loss achieved after sleeve gastrectomy was associated with modest but statistically significant changes in selected ventricular repolarization parameters assessed by surface ECG. Although all measured indices remained within generally accepted physiological ranges, post-operative reductions observed in QTc, QTd, JTc, Tp-e/QT, and QRSd/QT suggest subtle electrophysiological adaptations following weight loss rather than overt alterations in myocardial conduction or repolarization.

The present results support the concept that weight loss following sleeve gastrectomy may be accompanied by limited but measurable reorganization of myocardial electrical properties detectable on surface ECG. Exploratory observations suggest that behavioral factors may modulate post-operative electrophysiological changes, warranting further investigation. However, given the retrospective design, short follow-up duration, and reliance on surface electrocardiographic markers, the long-term clinical and arrhythmic implications of these electrophysiological changes remain uncertain. Larger, prospective studies with longer follow-up and comprehensive physiological assessments are required to further clarify the relationship between sleeve gastrectomy, weight loss, and ventricular repolarization dynamics.

DECLARATIONS

Ethics Committee Approval: The study was approved by the Gaziantep University Clinical Research Ethics Committee (Decision No: 2023/244, Date: 29.08.2023).

Informed Consent: Due to the retrospective nature of the study and the use of anonymized data, the requirement for written informed consent was waived by the institutional ethics committee.

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Author Contributions: Concept – LY, AA, MS; Design – LY, AA, MS; Supervision – LY, MS; Resources – LY; Materials – LY, AA; Data Collection and/or Processing – LY, AA, MS; Analysis and/or Interpretation – BKU, MS, VD, OB; Literature Review – BKU, LY; Writing – BKU, LY, MS, VD, AA, OB; Critical Review – BKU, MS, VD.

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ORIGINAL ARTICLE

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Impact of Hand Grip Strength on the Clinical Course of Patients with Acute Variceal Bleeding: A Single-Center Prospective Observational Study

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ABSTRACT

Objective: This study aimed to assess handgrip strength (HGS) in patients with acute variceal bleeding (AVB) following endoscopic therapy, compare it with compensated cirrhotic patients, and investigate its association with clinical outcomes, including rebleeding and short-term mortality.

Materials and Methods: In this single-center, prospective observational study, 34 AVB patients and 21 compensated cirrhotic were enrolled between May 2025-September 2025. Exclusion criteria included hepatocellular carcinoma, hepatic encephalopathy, malignancies, major organ failure, cerebrovascular disease, or neuromuscular disorders. HGS was measured using a digital dynamometer at discharge for AVB patients and during outpatient visits for controls. Baseline demographics, laboratory data, Child–Turcotte–Pugh (CTP) and model for end-stage liver disease (MELD-Na) scores, and 6-week outcomes were recorded. Statistical analyses compared HGS and clinical parameters between groups and evaluated correlations.

Results: HGS was significantly lower in the AVB group compared with compensated cirrhotic (p=0.0004). Within 6 weeks, nine patients experienced rebleeding, and seven patients died. Those with adverse outcomes demonstrated significantly reduced HGS, lower albumin, hemoglobin, and blood pressure, and higher MELD-Na and CTP scores. HGS negatively correlated with prognostic scores, hospital stay, international normalized ratio, and bilirubin, while positively correlating with albumin.

Conclusion: HGS is markedly reduced in patients with AVB and is associated with rebleeding, short-term mortality, and prolonged hospitalization. As a simple bedside measure of sarcopenia and nutritional status, HGS may serve as a valuable prognostic marker. Early identification of low HGS can guide nutritional and rehabilitative interventions to potentially improve outcomes in this high-risk patient population.

Keywords: Acute variceal bleeding, Hand dynamometer, Mortality, Muscle strength, Rebleeding, Sarcopenia

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INTRODUCTION

Acute variceal bleeding (AVB) represents a medical emergency, carrying a 6-week mortality rate of 10–20%.[1] Even patients who survive an initial acute bleeding episode remain at high risk, with rebleeding and mortality rates reaching approximately 60% and 33%, respectively, within the 1st year in the absence of secondary prophylaxis.[2] The combined use of non-selective β-blockers and endoscopic therapy has been shown to reduce the risk of rebleeding and improve survival outcomes.[3] Nevertheless, studies indicate that the risk of recurrent bleeding after endoscopic treatment remains between 7.8% and 29%, and fatal rebleeding events may still occur.[4] Thus, identifying risk factors that can predict poor outcomes in patients undergoing endoscopic therapy is of critical clinical importance.[5]

Malnutrition and sarcopenia are major complications of decompensated cirrhosis, primarily arising from metabolic dysfunction and nutritional imbalance.[6] Therefore, timely identification of prognostic indicators in cirrhotic patients is essential to improve outcomes in this vulnerable population. Muscle function has been shown to be strongly linked to both the progression and prognosis of cirrhosis.[7] In particular, handgrip strength (HGS), measured with a dynamometer, has been proposed as a sensitive marker of muscle function, with advantages including simplicity, feasibility, and good reproducibility. Patients with cirrhosis demonstrate markedly lower HGS compared to non-cirrhotic individuals[8] and reduced HGS has been validated as being associated with disease severity, malnutrition, sarcopenia and progression.[9,10]

The presence of substantial evidence demonstrating that sarcopenia and reduced HGS are associated with poor prognosis in liver cirrhosis has raised the necessity of investigating HGS in patients with AVB and its potential relationship with clinical outcomes. To date, only a limited number of studies have assessed HGS in patients undergoing endoscopic therapy for AVB. In our study, we aimed to evaluate HGS in patients with AVB compared with compensated cirrhotic patients, and to investigate the association of HGS, a bedside tool, with post-endoscopic clinical course, including rebleeding and related outcomes.

MATERIALS AND METHODS

Study Population

For our study, patients who presented to Samsun Training and Research Hospital between May 2025-September 2025 with a diagnosis of variceal bleeding or compensated liver cirrhosis were evaluated. The patient group consisted of cases with AVB, while the control group included compensated cirrhotic patients attending the gastroenterology outpatient clinic. Patients without AVB on endoscopy, as well as those with concomitant hepatocellular carcinoma, hepatic encephalopathy (HE), other malignancies, cardiac or renal failure, history of cerebrovascular disease, or neuromuscular disorders, were excluded from the study. Following these criteria, a total of 34 patients with AVB were enrolled as the patient group, and 21 compensated cirrhotic patients without any prior variceal bleeding were included as the control group. All patients underwent standard initial management in the emergency department, which included intravenous (IV) fluid replacement, blood transfusion to maintain hemoglobin (Hb) levels above 8 g/dL, prophylactic antibiotics (ceftriaxone 1 g IV), and administration of terlipressin. Emergency endoscopy was carried out within 12 h in every case. Patients presenting with hematemesis, melena, or hematochezia, together with a Hb drop and endoscopic evidence of actively bleeding varices or the presence of a nipple sign, were categorized as having AVB. The diagnosis of cirrhosis had been confirmed in all participants by abdominal ultrasonography performed within the preceding 6 months. Patients were hospitalized for a minimum of 5 days and monitored for at least 6 weeks, during which episodes of rebleeding and mortality were documented.

Clinical, Laboratory and HGS Assessment

Demographic characteristics, endoscopic findings, cirrhosis etiology, baseline biochemical parameters, endoscopic interventions, and length of hospital stay were collected. Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD-Na) scores were calculated using admission data.

The CTP score was determined based on bilirubin, albumin, international normalized ratio (INR), and the presence and severity of ascites and encephalopathy, as previously described.[11] The MELD-Na score was calculated using the formula: MELD + 1,32 × (137−Na)−(0.033×MELD×[137−Na]).[11,12]

HGS was measured using a digital hand dynamometer (Camry Digital Hand Dynamometer, Model: EH101, Fig. 1), which has been validated for clinical use.[13] Participants were instructed to sit upright in a chair with a backrest but without armrests, maintaining both feet flat on the floor and knees flexed at 90°. The test arm was positioned with 90° elbow flexion and the forearm in a neutral pronation-supination position.[14] Before the test, the procedure was explained, and a blinded examiner provided standardized verbal encouragement for participants to exert their maximum grip strength with the dominant hand. Three trials were performed with a 1-min rest interval, and the highest value, expressed in kilograms, was recorded. In the patient group, measurements were performed immediately before hospital discharge, following endoscopic control of variceal bleeding and completion of inpatient treatment. In the control group, measurements were obtained during outpatient clinic visits.

Figure 1. Camry EH101 dynamometer.

First, the baseline biochemical and demographic characteristics, as well as HGS, were compared between the AVB group and the compensated cirrhosis control group. Rebleeding was defined as new onset hematemesis, melena, or hematochezia, with endoscopic evidence of recurrent bleeding. Post-discharge, 6 weeks rebleeding or mortality were recorded. Then, patients were grouped according to the presence or absence of in 6 weeks rebleeding, or mortality, and their CTP, MELD, and hand grip strength scores were compared.

Ethical Approval

This study was approved by the Ethics Committee of Samsun University Non-Interventional Clinical Research (approval date: May 23, 2025). All participants were fully informed about the study procedures, and written informed consent was obtained in accordance with the Declaration of Helsinki.

Statistical Analysis

Descriptive statistics for numerical variables were presented as mean ± standard deviation and median, while categorical variables were summarized as counts and percentages. Group comparisons for normally distributed continuous variables were carried out using the independent samples t-test, whereas the Mann–Whitney U test was employed for non-normally distributed variables. Categorical variables were compared between groups using Pearson's Chi-square test. Correlation analyses were performed using Spearman's rank correlation test.

RESULTS

The mean age and sex distribution of the 34 patients with AVB and the 21 patients with compensated liver cirrhosis in the control group were comparable (Table 1). Regarding cirrhosis etiology, hepatitis B infection was predominant in the AVB group, whereas steatotic liver disease was more frequent in the compensated cirrhosis group (Table 1). As shown in Table 1, the most common site of varices in the AVB group was the cardia and esophagus gastro-esophagial varices-1, while esophageal varices were most frequent among compensated cirrhosis patients. Other demographic variables and the types of interventions performed for variceal bleeding are presented in Table 1.

Table 1. Characteristics and demographic data of all studied patients

Variable	Number/mean (%)	
	Acute variceal bleeding group n=34	Compensated cirrhosis group n=21
Age	57.2	60.2
Male: Female	26 (76):8 (24)	16 (77):5 (23)
Etiology		
MASLD	12 (35)	8 (38)
HBV	13 (38)	7 (33)
Alcohol	2(5)	4 (19)
PBC-AIH	2 (5)	1 (4)
Other	5 (14)	1 (4)
Location of varices		
Esophagus	14 (41)	19 (90)
GOV-1	16 (47)	2 (21)
GOV-2	3 (8)	-
IGV-1	1 (2)	-
Grade of varices		
F3	31(91)	1 (4)
F2	3 (8)	16 (74)
F1	-	4 (19)
Ascites +	17 (50)	-
Endoscopic procedure		
Band ligation	30 (88)	-
Histoacryl injection alone	3 (8)	-
Combined treatment	1 (2)	-

MASLD: Metabolic associated steatotic liver disease, HBV: Hepatitis B virüs, PBC-AIH: Primary biliary cholangitis-autoimmune hepatitis, GOV: Gastroesophageal varices, IGV: Intragastric varices.

When comparing baseline biochemical parameters between the AVB and compensated cirrhosis groups, platelet count, albumin, Hb, systolic blood pressure, and HGS were significantly lower in the AVB group, whereas bilirubin, ALT, CTP, and MELD-Na scores were significantly higher (Table 2).

Within 6 weeks after discharge, a total of nine patients experienced rebleeding. In this subgroup, MELD-Na scores were significantly higher, and HGS was significantly lower (Table 3). Furthermore, platelet count, Hb, and initial systolic blood pressure were significantly reduced in patients with rebleeding (Table 3).

During the 6-week follow-up, seven patients with AVB died. In those who died, baseline bilirubin, ALT, creatinine, and MELD-Na scores were significantly higher, while systolic blood pressure, albumin, diastolic blood pressure, and HGS were significantly lower (Table 4).

Table 2. A comparison of basic parametric and handgrips of the groups

Variables	Acute variceal bleeding group n=34 mean±SD	Compensated cirrhosis group n=21 mean±SD	*p*
Age, year	57.2±13	60.2±9	0.25
Male: Female*	26:8	16:5	0.98
WBC	7400±4400	6470±2280	0.28
Hemoglobin g/dL	7.6±1.8	10.6±1.4	**0.000**
Platelet	90.000±57.000	115.000±185.000	**0.02**
INR	1.35±0.21	1.31±0.2	0.48
Total bilirubin mg/dL	2.76±5.1	0.85±0.4	**0.01**
ALT IU	26±20	19.2±11.4	**0.02**
Albumin g/dL	2.7±0.4	3.5±0.5	**0.000**
Creatinine mg/dL	0.97±0.4	0.75±0.2	**0.02**
Sodium mg/dL	133±4.3	137±2.9	**0.000**
Systolic blood pressure mm/Hg	106±23	120±12	**0.01**
Diastolic blood pressure mm/Hg	60.7±10	63.8±8	0.24
Pulse, min	91±11	85±6	**0.01**
CTP	7.5±1.4	6.1±1.2	**0.000**
MELD-Na	15.7±7.6	11.5±3.1	**0.003**
Handgrip (kg)	20.9±12	29±7	**0.004**

WBC: White blood count, INR: International normalized ratio, ALT: Alanine aminotransferase, CTP: Child-Pugh score, MELD: Model for end-stage liver disease, SD: Standard deviation

Table 3. The comparison of the groups in terms of rebleeding in 6 weeks

Acute variceal bleeding group	Rebleed in 6 weeks n=9 mean±SD	Not rebleed in 6 weeks n=25 mean±SD	*p*
Age, year	57.4±16.2	57.2±12.1	0.9
Hemoglobin g/dL	6.1±0.9	8.1±1.7	**0.000**
Platelet×10^3	58.6±18.6	101±62.2	**0.004**
INR	1.4±0.25	1.3±0.2	0.4
Total bilirubin mg/dL	2.6±2.4	2.7±5.8	0.9
ALT IU	32.6±20	23.8±14.6	**0.007**
Albumin g/dL	2.4±0.2	2.9±0.4	**0.001**
Creatinine mg/dL	0.9±0.3	0.9±0.4	0.8
Systolic blood pressure mm/hg	93±16	110±23	**0.02**
Diastolic blood pressure mm/hg	55±9	62.8±10.9	0.06
CTP	8.1±1.2	7.3±1.4	0.1
MELD-Na	18.3±10.8	14.8±6.1	**0.003**
Handgrip (kg)	13.4±4.5	23.6±12.9	**0.02**

WBC: White blood count, INR: International normalized ratio, ALT: Alanine aminotransferase, CTP: Child-Pugh score, MELD: Model for end-stage liver disease, SD: Standard deviation

In addition, significant correlations were observed between HGS and several clinical parameters in the AVB group. Specifically, decreasing HGS was associated with longer hospital stay, as well as higher MELD-Na and CTP scores. Negative correlations were identified between HGS and INR, and total bilirubin, while a positive correlation was observed between HGS and albumin (Table 5).

DISCUSSION

In our study, we investigated whether HGS was lower in patients with AVB compared with those with compensated cirrhosis, and whether HGS was associated with the clinical course of these patients. HGS was found to be significantly lower in the AVB group compared to the compensated cirrhosis group. Moreover, among patients with AVB who were discharged, those who experienced rebleeding or death within 6 weeks had lower HGS values. In addition, HGS demonstrated negative correlations with prognostic scores such as CTP and MELD-Na, as well as with the length of hospital stay. Taken together, these findings suggest that HGS, a simple bedside tool for the assessment of sarcopenia and malnutrition in cirrhotic patients, is lower in those with AVB and may be associated with poorer clinical outcomes and longer hospital stay.

AVB is one of the most important causes of decompensation in chronic liver disease due to its substantial risk of morbidity and mortality. The early identification of patients at high risk for rebleeding and mortality during follow-up, as well as the use of tools that can help predict clinical outcomes, may provide significant advantages in clinical practice. Therefore, the early recognition of malnutrition and sarcopenia – both major contributors to decompensation and mortality in cirrhosis that also worsen clinical outcomes – is crucial in detecting and managing this vulnerable patient population.[7]

Sarcopenia is characterized by a reduction in skeletal muscle mass along with a decline in muscle function, which may be reflected as reduced strength or diminished physical performance.[15] In patients with liver cirrhosis, the prevalence of sarcopenia has been reported to range between 30% and 70%, varying according to the assessment method applied and the stage of liver disease.[16] Both sarcopenia and malnutrition become more common as liver disease progresses, with a higher frequency observed among male patients.[17] The underlying mechanisms of sarcopenia in cirrhosis are multifactorial, including inadequate dietary intake, malabsorption, metabolic disturbances, hormonal alterations, hyperammonemia, and increased muscle degradation.[17] Sarcopenia contributes to a higher incidence of complications such as infections, HE, and ascites.[18] Furthermore, it is recognized as an independent predictor of mortality in cirrhotic individuals.[19] Malnutrition and sarcopenia together are linked to elevated risks of decompensation, infection, and increased mortality among patients awaiting liver transplantation.[19] The HGS test has been considered a useful and sufficient tool for assessing sarcopenia in patients with hepatitis C infection, steatotic liver disease, and cirrhosis.[9,20,21] In our study, HGS was found to be markedly lower in the group with decompensated cirrhosis due to variceal bleeding compared with patients with compensated cirrhosis. Consistent with the literature, sarcopenia and malnutrition are known to accelerate the progression toward decompensation.[18,21]

Table 4. The comparison of the groups in terms of mortality in 6 weeks

Acute variceal bleeding group	Mortality in 6 weeks *n*=7 mean±SD	Survive in 6 weeks *n*=27 mean±SD	*p*
Age	**59.4±7.6**	**56±14.2**	0.5
Hemoglobin g/dL	6.9±1.2	7.8±1.9	0.1
Platelet×10^3	88±40	90±61	0.9
INR	1.4±0.2	1.3±0.2	0.2
Total bilirubin mg/dL	7.5±9.8	1.5±1.6	0.000
ALT, IU	51±30	19±10	0.001
Albumin g/dL	2.3±0.3	2.8±0.4	0.009
Creatinine mg/dL	1.1±0.6	0.9±0.3	0.02
Systolic blood pressure mm/hg	82.7±5.6	112±22	0.03
Diastolic blood pressure mm/hg	50±5	63.5±10.3	0.01
CTP	8.2±1.7	7.3±1.3	0.6
MELD-Na	19.2±10.6	14.8±6.5	0.01
Handgrip (kg)	10.4±5.2	23.7±12	0.000

WBC: White blood count, INR: International normalized ratio, ALT: Alanine aminotransferase, CTP: Child-Pugh score, MELD: Model for end-stage liver disease, SD: Standard deviation.

In a study evaluating sarcopenia, mortality, and the risk of rebleeding in patients with AVB, it was demonstrated that those with sarcopenia at the time of bleeding had a significantly higher risk of rebleeding within 2 years.[5] However, no association between sarcopenia and mortality was observed in the same study. Consistent with these findings, our study also revealed markedly lower HGS in the group that experienced rebleeding within 6 weeks.

The mechanism by which sarcopenia adversely influences variceal bleeding remains not fully elucidated. Clinically, the severity of portal hypertension represents the most significant predictor of AVB. From a pathophysiological perspective, the association between sarcopenia and portal hypertension may be reciprocal.[22] Factors linked to portal hypertension, such as

Table 5. The correlation analysis of the hand grip strength for some parameters

Spearman's Rho for hand grip strength	Age	Platelet	Albumin	Total bilirubin	CTP	BMI	MELD-Na	INR	Hb	ALT	Hospital stay
Correlation coefficient	–0.24	–0.29	0.78	–0.49	–0.61	0.11	–0.56	–0.32	–0.29	–0.11	–0.49
Sig	0.17	0.08	**0.000**	**0.003**	**0.000**	0.52	**0.001**	**0.05**	0.09	0.52	**0.003**

CTP: Child-Pugh score, MELD: Model for end-stage liver disease, BMI: Body-mass index, Hb: Hemoglobin, ALT: Alanine aminotransferase, INR: International normalized ratio

spontaneous portosystemic shunt formation, endotoxemia, and hyperammonemia, play a key role in promoting sarcopenia among cirrhotic patients.[23] Nevertheless, the specific contribution of sarcopenia to portal hypertension-related complications, including variceal bleeding, is still under debate. Skeletal muscle is recognized as an endocrine organ capable of secreting cytokines and polypeptides with autocrine, paracrine, and endocrine actions, many of which are critically involved in inflammatory pathways.[24] Consequently, sarcopenia may foster chronic low-grade inflammation, which tends to worsen with increasing portal hypertension and circulatory impairment, thereby heightening the risk of complications such as variceal bleeding.

The principal limitations of this study include the relatively small sample size and its single-center nature, which may restrict the generalizability of the findings. Nonetheless, a notable strength is that it represents one of the few studies to evaluate HGS specifically in patients presenting with AVB.

CONCLUSION

Since HGS is an indicator of both nutritional status and sarcopenia, this study highlights the importance of early screening and timely nutritional support in patients with AVB. Such interventions, including appropriate dietary strategies and exercise programs, may enhance muscle mass and ultimately improve clinical outcomes.

DECLARATIONS

Ethics Committee Approval: This study was approved by the Ethics Committee of Samsun University Non-Interventional Clinical Research (Date: 05.03.2025, Decision no: 2025/5/23).

Informed Consent: Written informed consent was obtained.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – HE, HD; Design – HE, HD; Supervision – HE; Resource – HE; Materials – HE; Data collection and/or processing – HE; Analysis and/or interpretation – HE, HD; Literature review – HE, HD; Writing – HE, HD; Critical review – HE, HD.

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Comparison of Tumor Markers and Risk of Malignancy Index in Borderline Ovarian Tumors

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ABSTRACT

Objective: Borderline ovarian tumors (BOTs) are non-invasive tumors with low malignancy potential frequently observed in patients of reproductive age. Therefore, pre-operative differential diagnosis is important in these patients. Our aim was to differentiate benign and BOTs preoperatively using risk of malignancy index (RMI) and tumor markers.

Materials and Methods: In our study, we retrospectively compared tumor markers and RMI of 85 patients aged between 17 and 84 years with post-operative benign (n=52) and borderline (n=33) ovarian cysts.

Results: In our study, the mean age of the benign group was significantly higher than the borderline group (p=0.001). Ca 125 and RMI values were significantly higher in the borderline group compared to the benign group (p=0.001 and p=0.018). In addition, mucinous tumors had significantly larger tumor diameter than serous tumors in the borderline group (p=0.022).

Conclusion: As a result of our study, since BOTs are seen in young patients of reproductive age, it may be suggested to use Ca125 and RMI for the differential diagnosis of benign and borderline cysts preoperatively.

Keywords: Borderline, Ca125, Menopause, Ovarian cysts, Ovarian neoplasms, Risk of malignancy index.

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INTRODUCTION

Borderline ovarian tumors (BOTs) were firstly described by Taylor in 1929[1] and later on categorized as epitelial ovarian tumor by International Federation of Gynecology and Obstetrics (FIGO) in 1971[2] and the World Health Organization in 2020.[3] BOTS are different type of tumors rather than benign or malignant ovarian tumors. They are also called "ovarian low malignant potential tumors"[4] but they are accepted as non-invasive, low malignant and atypically proliferated tumors and consist 15–20% of all primary ovarian neoplasms.[5,6] Due to presence BOTs in young ages, fertility preserving treatments are the major treatment offers for patients.[7]

These young patients need to precise pre-operative diagnosis for their ovarian masses. Ultrasonographic scanning and tumor markers are the major diagnostic tools for the prediction of ovarian masses. For the differential diagnosis between benign and malignant adnexial masses, a combination of various markers is often used, such as the risk of malignancy

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index (RMI). RMI is an easy, simple, and advicable method to differentiate malignant and benign adnexial masses.[8] RMI is a numeric value which is calculated with the combination of serum Ca125 level, menopausal state, and ultrasonographic findings, and modified to four different versions.[9-12]

In our study, we tried to find out whether the RMI 1 and serum biomarkers differences between benign and BOTs to facilitate pre-operative evaluation and differentiation of ovarian masses.

MATERIALS AND METHODS

Totally 85 patients aged between of 17 and 84 who were selectively operated for suspected adnexal mass in our clinic between 2016 and 2020 and resulted in BOT and benign ovarian tumor as pathologies were retrospectively included in our study. We divided to patients to benign (*n*=52) and borderline (*n*=33) groups. The study was approved by the İstanbul Medeniyet University ethics committee (date: 02.09.2020, decision no: 2020/0571) and had been performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

Pre-operative ultrasonographic examinations were performed in all patients participating in the study. Age, parity, menopausal status, alpha-fetoprotein (AFP) (ng/mL), Ca125 (U/mL), Ca15-3 (U/mL), Ca19-9 (U/mL), Carcinoembryonic antigen (CEA) (ng/mL) values, ultrasonography findings (multiloculation, solid field or papillary protrusion, bilaterality, mass diameter), pre-operative neutrophil/lymphocyte ratios (NLR), frozen pathology and final pathology results were recorded. The patient's ultrasonographic findings, Ca-125 serum level, and menopausal status were scored, and RMI values were calculated numerically (as RMI 1=Ultrasonography score [U score] × Menopause score [M score] × CA-125 level [mIU/mL]). The patients whose records were incomplete or whose RMI calculation could not be performed had been excluded from the study. After RMI was calculated, the results were compared with histopathological results.

Statistical Analysis

Analyses the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) was evaluated in 22 package programs. In the study, descriptive data were shown with n. % values in categorical data, mean ± standard deviation, and median interquartile range (25–75 percentile values) values in continuous data. Chi-square analysis (Pearson Chi-square) was applied to compare categorical variables between groups. The conformity of continuous variables to normal distribution was evaluated by the Kolmogorov-Smirnov test. The Mann–Whitney U-test was used to compare the pairwise groups. The Spearman correlation test was used to examine the relationship between continuous variables. In the analyzes, the statistical significance level was accepted as $p<0.05$.

RESULTS

The age of the patients who were in benign group was significantly higher than the patients who were in borderline group ($p=0.001$). Furthermore, Ca 125 ($p=0.001$) and RMI score ($p=0.018$) were found to be significantly lower than borderline patients. While 69.4% of menopausal women had benign masses, 55.1% of premenopausal women had benign final pathology, and there was no significant difference between them (p=0.180). There was no significant difference between the last pathology in terms of other parameters (p>0.05) (Table 1).

Table 1. Comparison of tumor markers, tumor sizes, N/L ratio, and RMI score by final pathology

	Benign (*n*=52) Median (IQR)	Borderline (*n*=33) Median (IQR)	*p*[a]
Age	49 (42–59.5)	36 (30–49)	**0.001***
Ca 125 (U/mL)	17.55 (10.90–30.00)	34.70 (16.30–86.00)	**0.001***
AFP (ng/mL)	2.90 (2.07–4.45)	2.15 (1.54–4.49)	0.203
Ca 15.3 (U/mL)	14.65 (9.80–19.40)	14.30 (10.30–19.10)	0.801
Ca 19.9	12.06 (7.05–22.52)	15.03 (8.43–24.30)	0.415
CEA (ng/mL)	1.50 (1.04–2.03)	1.48 (1.09–2.29)	0.399
RMI score	43.10 (0.00–72.90)	72.90 (16.00–717.00)	**0.018***
Diameter	8.00 (6.00–11.25)	8.50 (8.00–13.00)	0.130
NLR	2.34 (1.67–3.22)	2.20 (1.86–2.87)	0.853
	***n* (%)**	***n* (%)**	
Menopausal status			
Menopause	25 (69.4)	11 (30.6)	0.180[b]
Premenopause	27 (55.1)	22 (44.9)	

[a]Mann–Whitney U test; [b]Chi-square analysis was applied; *$p<0.05$. N/L: Neutrophil/lymphocyte, RMI: Risk of malignancy; IQR: Interquartile range; Ca: Cancer antigen; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; NLR: Neutrophil lymphocyte ratio.

Table 2. Comparison of tumor markers, tumor sizes, N/L ratio and RMI score by tumor type

	Mucinous (*n*=11) Median (IQR)	Serous (*n*=17) Median (IQR)	*p*[a]
Ca 125 (U/mL)	25.95 (16.00–40.10)	80.30 (21.55–324.85)	0.135
AFP (ng/mL)	1.98 (1.55–3.14)	2.02 (1.46–4.28)	0.879
Ca 15-3 (U/mL)	11.05 (8.50–16.20)	15.05 (13.80–19.50)	0.109
Ca 19.9	16.69 (1.10–21.82)	15.09 (8.43–24.30)	0.892
CEA (ng/mL)	1.35 (1.04–2.38)	1.67 (1.09–2.29)	0.841
RMI score	37.45 (10.40–248.40)	175.20 (39.85–989.50)	0.087
Diameter	20.00 (8.00–20.00)	8.00 (7.50–9.00)	**0.022***
NLR	2.10 (1.80–3.40)	2.25 (1.97–2.98)	0.578

[a]Mann–Whitney U test was applied; *$p<0.05$. N/L: Neutrophil/lymphocyte; RMI: Risk of malignancy; IQR: Interquartile range; Ca: Cancer antigen, AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; NLR: Neutrophil lymphocyte ratio.

The tumor diameter of mucinous tumors was found to be significantly higher than in serous patients (p=0.022). There was no significant difference between tumor types in terms of other parameters ($p>0.05$) (Table 2).

In the correlation analysis performed in the borderline group, a significant positive correlation was observed between the RMI score and Ca 125. There is a significant positive correlation between Ca 125 and Ca 15.3. A significant positive correlation was found between age and parity (Table 3).

DISCUSSION

Adnexial masses are the most common reason for gynecologic oncology referral. Because ovarian carcinoma, which is the most mortal cancer of female reproductive system, should be ruled out.[13] Due to the fact that the discrimination of the masses, benign or malignant, is really important. BOT is a tumor between benign and malignant tumors[14] and staged according to FIGO staging system for epithelial ovarian carcinoma.[15] In our study, we compared borderline tumors with benign adnexial masses and found out that borderline group is younger than benign group. Due to the presence of BOT in reproductive-aged patients, fertility-conserving treatment of the BOT should dominantly considered, but the recurrence rates are higher and mostly benign in early stage BOT's patients.[14,16]

For the differentiation of the BOT from benign masses, ultrasonographic findings and serum tumor markers are used frequently. In our study, Ca125 levels, age, and RMI values in the BOT group are higher than benign group. Ca 125 is a precious marker for predicting benign or borderline tumors, but not alone.[17] RMI combines ultrasonographic findings, menopausal status, and Ca 125 levels and considers malignancy risk of the masses.[9] Moreover, there are 4 different types for RMI (1–4) which are considering different numeric status for each counting parameters. In the comparison of RMI1-4 for differentiation on of BOT's from benign ovarian tumors, RMI 1 was the best method when compared with the other RMI methods.[18] Hence, in our study, we also calculated RMI1 for comparing the groups. For the menopausal status we could not find any difference between our study groups. However, a significant difference was found between the two groups in terms of age. In literature, almost 30% of BOTs occur in women of reproductive age under 40 years of age, as in our study.[19]

Furthermore, we made subdivision for our BOTs according to their histologic typing to serous and mucinous group. In literature, Ca 125 level especially is higher in serous group than mucinous, but Ca 19-9 level is higher in mucinous group than serous.[20,21] However, in our study, we could not find any difference for Ca125 or 19-9 levels between serous and mucinous groups. However, we found significantly larger cysts in mucinous borderline group than serous as in literature.[22,23] And also mucinous BOTs are commonly unilateral and have a higher invasive occurrence rate than serous type.[16,23] Due to the fact that salpingo-oophorectomy is recommended for mucinous subtype of BOTs. Hence, pre-operative decision of the type of adnexial masses is extremely important.

In our study, in the borderline group, RMI and Ca 125 values showed a positive correlation. In the literature, increased values of Ca 125 were observed, especially in serous BOT,[24] but in our study, no significant difference was found between serous and mucinous BOT. In studies, it has been observed that Ca 125 value and Ca 19-9 value were also found to be high in BOTs.[21] In our study, we observed a positive correlation between Ca125 and Ca 15-3 among BOTs. Further studies are needed to see whether there is an increase in Ca 15-3 with an increase in Ca 125 in the BOT group.

Table 3. Correlation analysis results (in borderline group)

	RMI	NLR	AFP	Ca 125	Ca 15-3	Ca 19.9	CEA	Diameter	Age
NLR									
r	0.337								
p	0.064								
AFP									
r	–0.252	0.150							
P	0.205	0.457							
Ca 125									
r	**0.668**	0.332	–0.126						
p	**0.000***	0.068	0.532						
Ca 15.3									
r	0.301	0.332	0.263	**0.367**					
p	0.100	0.068	0.184	**0.042***					
Ca 19.9									
r	–0.109	0.341	–0.225	0.067	0.174				
p	0.567	0.065	0.269	0.724	0.357				
CEA									
r	–0.258	–0.192	0.069	–0.028	0.059	–0.058			
p	0.176	0.319	0.731	0.885	0.760	0.768			
Diameter									
r	0.208	0.089	–0.034	0.087	0.093	0.102	**–0.468**		
p	0.261	0.622	0.868	0.642	0.618	0.593	**0.010**		
Age									
r	0.179	0.205	–0.020	–0.021	0.187	–0.051	0.071	0.066	
p	0.334	0.253	0.921	0.909	0.313	0.787	0.714	0.714	
Parity									
r	0.153	0.334	–0.034	–0.022	0.018	–0.074	0.097	0.007	**0.657**
p	0.412	0.057	0.865	0.907	0.923	0.697	0.617	0.970	**0.000***

**p*<0.05. N/L: Neutrophil/lymphocyte; RMI: Risk of malignancy; IQR: Interquartile range; Ca: Cancer antigen; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; NLR: Neutrophil lymphocyte ratio.

Furthermore, we tried to find out whether any differences also in CEA, AFP, and NLR values between groups, but there were not any significance. Based on the data in the literature that pelvic inflammatory disease increases the risk of ovarian cancer,[24] we used NLR to investigate whether there is a different inflammatory process in BOTs, but we could not obtain a significant result.

CONCLUSION

While there are studies showing that even benign ovarian tumors increase the risk of borderline tumor in the long term,[25] it may be helpful to consider Ca 125 and RMI values in order to make a differential diagnosis of benign-BOT while preoperatively evaluating this group of patients in reproductive age. More studies are needed to determine other factors that may be helpful for differential diagnosis.

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Ethics Committee Approval: This study was approved by the İstanbul Medeniyet University (Date: 02.09.2020, Decision no: 2020/0571).

Informed Consent: It is a retrospective study.

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Age-Related Prognostic Factors and Survival Outcomes in Ewing Sarcoma: A Single-Center Experience

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ABSTRACT

Objective: To evaluate age-related prognostic differences in Ewing sarcoma (ES) patients and identify clinical factors influencing outcomes in a tertiary care setting.

Materials and Methods: Seventy-six patients with ES (ages 1–78) treated between 2010 and 2024 were reviewed retrospectively. Clinical features and treatments were compared across four age groups (0–9, 10–17, 18–25, and ≥25 years). Overall survival (OS) and disease-free survival (DFS) were estimated using Kaplan–Meier curves and compared with log-rank tests.

Results: There were no statistically significant differences in 10-year OS or DFS between age groups ($p>0.05$), although patients ≥18 years showed a trend toward worse survival. The presence of metastases at diagnosis was associated with markedly lower survival (5-year OS 20–30% vs. 70% for localized disease). Patients who underwent surgical resection of the primary tumor had significantly better survival than those managed without surgery, while limb-salvage versus amputation showed no difference in outcomes. Relapse was associated with poor prognosis.

Conclusion: Adult ES patients tend to have poorer outcomes than children, though age alone was not a significant predictor in this series. Achieving effective local control with surgery and addressing metastatic disease remain critical to improving survival.

Keywords: Age groups, Ewing sarcoma, Metastasis, Prognostic factors, Surgery, Survival

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INTRODUCTION

Ewing sarcoma (ES) is a rare, aggressive neuroectodermal malignancy that typically affects the bones and soft tissues of children and adolescents.[1,2] Although mainly a pediatric disease, it can also occur in adults, where it often presents with distinct features and worse outcomes.[3,4]

The prognosis of ES depends on age, tumor site, metastatic status, and treatment response.[5,6] In localized disease, modern treatment protocols have improved the 5-year overall survival (OS) rate to 70–80%.[6] However, metastatic disease is associated with a poor 5-year survival rate of approximately 30%.[5] Tumor sites typically include long bones of the extremities or the pelvis, with pelvic localization linked to worse outcomes due to larger tumor volumes and challenges in achieving local control.[6,7]

Age remains a key prognostic factor in ES. Adolescents, young adults, and especially those over 40 have poorer survival than children. They often present with metastatic disease, experience more treatment-related toxicity, and have lower survival, possibly due to biological differences, comorbidities, or difficulty tolerating intensive therapy.[3,4,8] Standard treatment includes neoadjuvant chemotherapy, local control through surgical resection and/or radiotherapy, and adjuvant chemotherapy.[5] However, age-related survival disparities persist, highlighting the need for further research into age-specific factors.

Much of the available literature on ES comes from pediatric populations treated in high-resource settings, while data on adult patients and from tertiary care centers in diverse socioeconomic contexts remain limited.[3,9] This retrospective study evaluates clinical characteristics and age-related prognostic differences in ES patients at a tertiary care center, analyzing tumor location, metastatic status, chemotherapy, radiotherapy, and surgical interventions to identify factors affecting survival and guide individualized treatment strategies.

MATERIALS AND METHODS

This retrospective observational study was conducted on patients diagnosed and treated for ES between 2010 and 2024. The study was reviewed and approved by the Metin Sabanci Baltalimanı Bone Diseases Hospital Institutional Ethics Committee (Meeting no: 28, Decision no: 193, and Date: October 28, 2024) and carried out in accordance with the principles of the Declaration of Helsinki. All data were obtained from existing medical records, with patient confidentiality preserved.

All patients who had been treated at our center and had a histopathologically confirmed diagnosis of ES were included. This definition encompassed both bone-origin tumors and extraskeletal ESs arising from soft tissue. Patients of all age groups and both sexes were included, regardless of metastatic status at presentation (localized or metastatic at diagnosis). After excluding patients with incomplete clinical data or unconfirmed diagnoses, a total of 76 patients were included in the study.

The diagnosis of ES was established through histopathological examination of tumor specimens. All tumors were confirmed as part of the ES family by characteristic light microscopic findings of small round cell malignancy and positive immunohistochemical staining (e.g., diffuse membranous CD99 positivity), supported by appropriate histological features. In selected cases, the diagnosis was further corroborated by molecular testing (e.g., *EWSR1* gene rearrangement analysis) when available. In this study, extraskeletal ES was defined as a tumor arising in soft tissues without bone involvement detected by imaging or surgery, whereas bone ES referred to cases involving a primary bone lesion. Only patients with a confirmed diagnosis of ES were included; other small round cell tumors were excluded or reclassified based on pathology results.

Detailed demographic and clinical data were collected from each patient's file. Recorded variables included age and sex at diagnosis, anatomical location of the tumor (bone or soft tissue), and the exact site of the primary tumor. The presence and location of distant metastases at diagnosis (lung, bone, or both) were documented. Disease extent at presentation was categorized as localized or metastatic. All patients were noted to have received multi-agent systemic chemotherapy according to standard ES protocols. Radiotherapy use was recorded as neoadjuvant or adjuvant. In addition, the type of surgical management for the primary tumor was documented for each patient.

Age at diagnosis was categorized into four groups (0–9, 10–17, 18–25, and ≥25 years) to align with pediatric, adolescent, young-adult, and adult clinical categories and to capture known age-related differences in the distribution of primary and metastatic sites in ES.[10] These age categories were chosen to reflect pediatric, adolescent, young adult, and older adult subgroups, enabling comparisons of outcomes between different age groups. Our hospital is a specialized orthopedic center that has been providing services in the field of bone and soft tissue tumor surgery for many years. Over the years, patients have been operated on by different experienced orthopedic oncology surgeons, all of whom have applied similar surgical approaches. Surgical treatment types were categorized as follows: (1) No surgical resection (systemic therapy ± radiotherapy only), (2) limb-sparing surgery with

adjunctive cryotherapy using liquid nitrogen, (3) limb-sparing resection with endoprosthetic reconstruction, (4) limb-sparing resection with biological or allograft reconstruction, (5) simple resection/curettage without major reconstruction, and (6) amputation. These groups were used to compare outcomes, such as survival or recurrence rates, by surgical modality. For outcome analyses, patients were also grouped according to survival status (alive vs. deceased) and event occurrence (recurrence or metastasis present vs. absent). Surgical margin status was not consistently documented across the entire cohort and was therefore not included as a predictor in the primary analyses. In our institutional practice, positive margins are generally managed with re-excision when feasible or with adjuvant radiotherapy.

All patients underwent comprehensive staging at diagnosis according to standard orthopedic oncology protocols. Baseline imaging included local radiological assessment of the primary tumor and distant metastasis screening. The local extent of the primary tumor (intraosseous spread and soft tissue extension) and its relationship to adjacent structures were evaluated using plain radiography and magnetic resonance imaging (MRI). Thoracic computed tomography (CT) was used to detect distant metastases, and positron emission tomography–CT (PET-CT) was used to survey for metastatic disease in bone or other sites. Staging results were used to classify patients as localized or metastatic. During treatment, imaging was also used to assess response (e.g., tumor shrinkage after neoadjuvant chemotherapy) and to guide surgical planning.

After completion of initial treatment, patients were followed clinically at regular intervals in accordance with our institutional follow-up protocols for ES. Follow-up evaluations typically included physical examination and appropriate imaging (e.g., thoracic CT, MRI of the primary site, PET-CT) to detect recurrence or metastasis. During follow-up, the occurrence and timing of distant metastases and local recurrences were recorded. Specifically, the time to metastasis for patients who developed metastatic disease during follow-up and the time to local recurrence were determined. For survival analysis, patient vital status at the last contact was recorded (alive or deceased) and, if applicable, the date of death was noted. OS was defined as the time from diagnosis to death from any cause or to the last known follow-up for living patients. Disease-free survival (DFS) was defined as the time from completion of primary treatment (definitive surgery or completion of initial therapy) to the first occurrence of either tumor recurrence (local relapse) or a new distant metastasis, or to the last follow-up for those without an event. Patients without an event were censored at their last disease-free follow-up visit. OS and DFS were calculated in months.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 29. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used to evaluate the study data. The normality of distribution for continuous variables was assessed using the Shapiro–Wilk test and graphical methods. The Mann–Whitney U test was used to compare two independent groups of continuous variables that were not normally distributed. The Pearson Chi-square test, Fisher's exact test, and Fisher–Freeman–Halton test were used to compare categorical variables. Survival outcomes were evaluated using the Kaplan–Meier survival analysis method, and comparisons between groups were performed using the log-rank test. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 76 patients were included, with a mean age of 17.7±12.1 years (range 1–78). Most patients (60.5%) were younger than 18 years. The median follow-up was 43.6 months. Mortality occurred in 40.8% (*n*=31), and extraskeletal involvement was present in 13.2% (*n*=10). At diagnosis, 10.5% (*n*=8) had distant metastases, most commonly in the lung. During follow-up, 11.8% developed metastasis and 9.2% experienced local recurrence.

All patients received neoadjuvant chemotherapy; 35.5% also received neoadjuvant radiotherapy, 36.8% adjuvant chemotherapy, and 3.9% adjuvant radiotherapy. Primary orthopedic treatments included systemic therapy only (26.3%), resection (25.0%), liquid nitrogen–treated autograft (19.7%), tumor prosthesis reconstruction (15.8%), other reconstructions (10.5%), and amputation (2.6%). Baseline patient and treatment characteristics are summarized in Table 1.

There was no statistically significant difference in mortality by age, tumor site, extraskeletal disease, radiotherapy, chemotherapy, or local recurrence ($p>0.05$). However, metastasis—either at presentation (77.8% vs. 29.3%, $p=0.001$) or during follow-up (87.5% vs. 35.8%, $p=0.02$)—was strongly associated with higher mortality. Patients experiencing any event (metastasis/recurrence) had significantly worse outcomes (73.9% vs. 26.4%, $p=0.001$). Importantly, survival differed by primary surgical approach ($p=0.001$): Patients treated with liquid nitrogen–treated autografts demonstrated markedly improved survival compared to those undergoing systemic therapy only, resection, or tumor prosthesis reconstruction (Table 2).

Survival Analysis

Of the 76 patients, 45 (59.2%) were alive, and 31 (40.8%) had died at last follow-up. The mean OS was 78.3 ± 5.6 months, with a 10-year OS rate of 49.7% (SE 7.1%) (Fig. 1).

Table 1. Distribution of descriptive characteristics

Age	
Mean±SD	17.7±12.1
Median (Min–Max)	15 (1–78)
0–9 years	12 (15.8)
10–17 years	34 (44.7)
18–25 years	20 (26.3)
≥25 years	10 (13.2)
Follow-up time (months)	
Mean±SD	54.62±37.42
Median (Min–Max)	43.6 (7–120)
Mortality	31 (40.8)
Extraskeletal involvement	10 (13.2)
Neoadjuvant chemotherapy	100 (100)
Neoadjuvant radiotherapy	27 (35.5)
Adjuvant chemotherapy	28 (36.8)
Adjuvant radiotherapy	3 (3.9)
Total metastasis	16 (21)
Lung	9
Bone	3
Lung + Bone	4
Initial disease stage	
Local disease	68 (89.5)
Metastatic disease	8 (10.5)
Metastasis during follow-up	8 (11.8)
Time to metastasis (months) (*n*=8)	
Mean±SD	17.8±11.7
Median (Min–Max)	16.5 (4–36)
Local recurrence	7 (9.2)
Time to recurrence (months) (*n*=7)	
Mean±SD	28.29±14.91
Median (Min–Max)	24 (14–52)
Type of primary orthopedic treatment	
Systemic therapy only (no surgery	20 (26.3)
Liquid nitrogen–treated autograft	15 (19.7)
Tumor prosthesis reconstruction	12 (15.8)
Resection (limb-sparing surgery)	19 (25.0)
Other reconstruction (bone graft/implant)	8 (10.5)
Amputation	2 (2.6)

SD: Standard deviation.

Table 2. Comparison of patient characteristics by survival status

	Mortality		
	Survivors (*n*=45)	**Non-survivors (*n*=31)**	***p***
Age at diagnosis			
Mean±SD	15.20±8.70	21.35±15.27	
Median (Min–Max)	14 (1-50)	18 (5-78)	
0–9 years	10 (83.3)	2 (16.7)	[a]0.157
10–17 years	21 (61.8)	18 (38.2)	
18–25 years	10 (50.0)	10 (50.0)	
≥25 years	4 (40.0)	6 (60.0)	
Tumor location			
Axilla (soft tissue)	1 (100.0)	0 (0.0)	[a]0.464
Foot (soft tissue)	0 (0.0)	1 (100.0)	
Femur	6 (46.2)	7 (53.8)	
Fibula	3 (42.9)	4 (57.1)	
Gluteal region (soft tissue)	0 (0.0)	2 (100.0)	
Humerus	3 (60.0)	2 (40.0)	
Calcaneus	2 (100.0)	0 (0.0)	
Clavicle	1 (100.0)	0 (0.0)	
Metatarsal	2 (66.7)	1 (33.3)	
Shoulder (soft tissue)	2 (100.0)	0 (0.0)	
Pelvis	5 (50.0)	5 (50.0)	
Radius	1 (100.0)	0 (0.0)	
Sacrum	3 (75.0)	1 (25.0)	
Scapula	3 (100.0)	0 (0.0)	
Tibia	10 (71.4)	4 (28.6)	
Ulna	1 (100.0)	0 (0.0)	
Thigh (soft tissue)	2 (50.0)	2 (50.0)	
Vertebra	0 (0.0)	2 (100.0)	
Follow-up duration (months)			
Mean±SD	70.71±37.52	31.27±22.01	[d]0.001**
Median (Min–Max)	70.2 (10–120)	24.5 (7-99)	
Ekstraskeletal involvement			
Absent	40 (60.6)	26 (39.4)	[b]0.732
Present	5 (50.0)	5 (50.0)	
Neoadjuvant radiotherapy			
Absent	31 (63.3)	18 (36.7)	[c]0.333
Present	14 (51.9)	13 (48.1)	

Table 2. Continue

	Mortality		
	Survivors (*n*=45)	Non-survivors (*n*=31)	*p*
Adjuvant chemotherapy			
Absent	26 (54.2)	22 (45.8)	[c]0.241
Present	19 (67.9)	9 (32.1)	
Adjuvant radiotherapy			
Absent	44 (60.3)	29 (39.7)	[b]0.563
Present	1 (33.3)	2 (66.7)	
Metastasis			
Absent	41 (70.7)	17 (29.3)	[c]0.001**
Present	4 (22.2)	14 (77.8)	
Initial stage			
Localized disease	43 (63.2)	25 (36.8)	[b]0.057
Metastatic disease	2 (25.0)	6 (75.0)	
Metastasis during follow-up			
Absent	43 (64.2)	24 (35.8)	[b]0.02*
Present	1 (12.5)	7 (87.5)	
Time to metastasis (months)			
Mean±SD	68.30±40.40	22.58±22.26	[d]0.001**
Median (Min–Max)	70.2 (0-120)	18 (0-99)	
Local recurrence			
Absent	43 (62.3)	26 (37.7)	[b]0.114
Present	2 (28.6)	5 (71.4)	
Time to recurrence (months)			
Mean±SD	69.50±37.97	29.71±21.26	[d]0.001**
Median (Min–Max)	70 (10–120)	23.2 (7-99)	
Any event (Metastasis or recurrence)			
Absent	39 (73.6)	14 (26.4)	[c]0.001**
Present	6 (26.1)	17 (73.9)	
Time to any event (months)			
Mean±SD	67.09±40.74	21.44±20.62	[d]0.001**
Median (Min–Max)	70 (0–120)	18 (0-99)	
Primary surgical treatment			
Systemic therapy only	6 (30.0)	14 (70.0)	[a]0.001**
Liquid nitrogen	15 (100.0)	0 (0.0)	
Tumor prosthesis	7 (58.3)	5 (41.7)	
Resection	11 (57.9)	8 (42.1)	
Reconstruction (other)	5 (62.5)	3 (37.5)	
Amputation	1 (50.0)	1 (50.0)	

[a]Fisher Freeman Halton test, [b]Fisher's Exact test, [c]Pearson Chi-square test, [d]Mann–Whitney U test, *p<0.05, **p<0.01. SD: Standard deviation.

Survival by Age Group

Kaplan–Meier survival analysis stratified by age group is summarized in Table 3.

When stratified by age, 10-year OS rates were 75.0% for patients aged 0–9 years, 49.9% for 10–17 years, 42.1% for 18–25 years, and 40.0% for ≥25 years, without a statistically significant difference between groups (Log-rank p=0.155) (Fig. 2).

DFS (Metastasis-and Recurrence-Free Survival)

Table 4 presents the DFS analysis by age group, considering any disease-related event (defined as the occurrence of metastasis or local recurrence) as the endpoint.

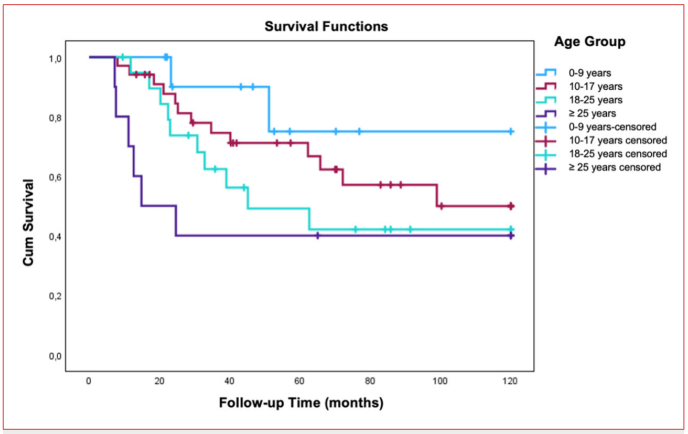

Figure 1. Overall survival curve. (X-axis: Follow-up time in months; Y-axis: Cumulative survival. The curve represents the Kaplan–Meier overall survival for all patients, with tick marks indicating censored observations).

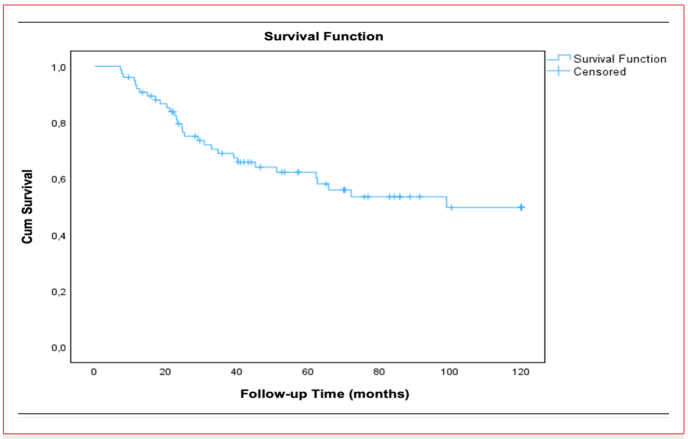

Figure 2. Kaplan–Meier overall survival curves by age group. (Survival curves are shown for each age category: 0–9 years, 10–17 years, 18–25 years, and ≥25 years. X-axis: Follow-up time in months; Y-axis: Cumulative survival probability. Tick marks on each curve indicate censored observations for that group).

Table 3. Survival analysis by age group

Age	*n*	Non-survivors	Survivors	Survival rate (%)	Mean survival time	95% Confidence interval
						Lower-upper
0–9 years	12	2	10	83.3	100.00±12.42	75.65–124.35
10–17 years	34	13	21	61.8	83.33±7.88	67.88–98.78
18–25 years	20	10	10	50.0	69.08±10.87	47.76–90.39
≥25 years	10	6	4	40.0	55.82±16.63	23.21–88.42

Kaplan–Meier analysis.

Table 4. Disease-free survival (recurrence+metastasis free) by age group

Age	*n*	Event (+)	Event (-)	10-year event-free survival rate (%)	Mean event-free survival (months±SE)	95% Confidence interval	
						Lower	Upper
0–9 years	12	4	8	66.7	79.75±16.36	47.69	111.82
10–17 years	34	9	25	73.5	89.54±8.70	72.49	106.59
18–25 years	20	7	13	65.0	76.70±12.61	51.98	101.41
≥25 years	10	3	7	70.0	84.76±16.72	52.00	117.53
Overall	76	23	53	69.7	84.38±6.14	72.36	96.41

Kaplan–Meier analysis. SE: Standard error

For DFS, 69.7% of patients remained free of recurrence or metastasis at 10 years. Mean DFS was 84.4±6.1 months, with no significant differences observed across age groups (Log-rank p=0.915) (Fig. 3).

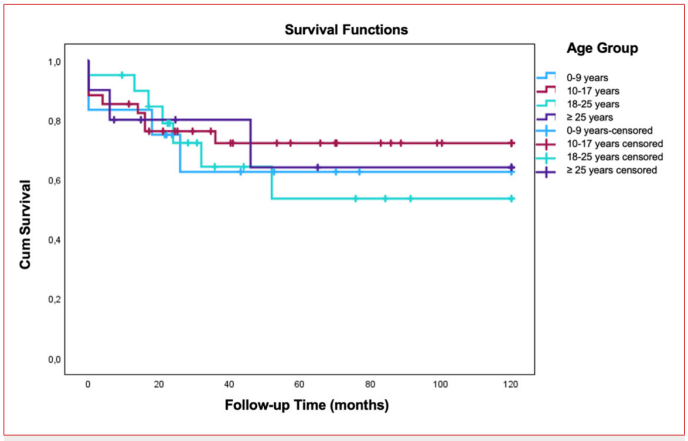

Figure 3. Kaplan–Meier disease-free survival curves by age group. (Curves represent metastasis- and recurrence-free survival for age groups 0–9, 10–17, 18–25, and ≥25 years. X-axis: Follow-up time in months; Y-axis: Cumulative proportion of patients without metastasis or recurrence. Tick marks indicate censored observations).

DISCUSSION

This study observed a trend toward worse survival outcomes in adult ES patients compared to pediatric patients, although age was not an independent predictor of survival in this cohort. The lack of a statistically significant correlation between age and oncological outcomes suggests that other factors, such as metastatic status or treatment modalities, may have a stronger influence on prognosis in our series. These findings align with larger population studies reporting poorer survival in adults, with 5-year survival rates of approximately 40–50% in adults versus 65–70% in children.[11,12] The inferior survival in older patients has been attributed to multiple factors, including more advanced disease at presentation and potential biological differences. Indeed, adults are more often diagnosed with metastases, axial or extraosseous primary tumors.[11,12] Some evidence suggests that when adults can be treated with the same intensive protocols as children, outcomes may improve, supporting aggressive therapy for fit adult patients.[13] Nonetheless, our findings reinforce the consistently poorer prognosis of adult ES and underscore the need for age-tailored strategies to close this survival gap.[11,12]

The presence of metastases at diagnosis was strongly associated with inferior outcomes in our study, in line with the well-established prognostic impact of metastatic disease.

[12] Patients who presented with metastases had markedly lower survival rates, roughly on the order of 20–30% 5-year OS, compared to about 70% in those with localized disease. [14] Notably, the site and extent of metastasis influence prognosis: Isolated pulmonary metastases carry a somewhat better outlook than extrapulmonary or combined metastases. [14] Prior cooperative group trials have reported around 30% long-term survival for patients with isolated lung metastases, whereas those with bone or bone marrow involvement fare significantly worse (often <20% survival).[14] Our findings are consonant with these patterns, as metastatic patients in our cohort had outcomes that reflect the lower end of survival expectations. This underscores that initial metastatic spread remains the strongest adverse predictor in ES, and despite modern multimodal therapy, improvements for this high-risk group have been minimal.[12] Aggressive systemic therapy (e.g., interval-compressed chemotherapy and consolidative whole-lung irradiation for lung metastases) is standard, yet clearly new approaches are needed to substantially improve survival in the metastatic setting.[14]

Our analysis of recurrence patterns highlights the dire prognosis associated with ES relapse. Among patients who experienced recurrence, the majority had distant metastatic relapse rather than isolated local failure, reflecting the tumor's aggressive biology. The post-relapse survival in our series was poor, which aligns with published data showing that fewer than 15% of patients survive 5 years after a recurrence.[14] In fact, large retrospective studies have reported 5-year post-relapse survival on the order of only ~10%.[14] Prognostic factors in the relapsed setting include the timing and location of recurrence. Patients who relapse more than 2 years after initial therapy, or with localized (or lung-only) recurrences, have a better chance of prolonged survival than those with early or multifocal relapse. [15] For example, one study noted 2-year post-relapse survival of ~40% for patients with late or lung-confined recurrence, versus under 10% in those with early or disseminated relapse. [15] These observations suggest that a subset of relapsed patients can achieve long-term remission with aggressive salvage treatments (such as surgery for solitary lesions, high-dose chemotherapy with stem cell rescue, or novel agents), but overall, refractory ES remains overwhelmingly lethal. Our findings reinforce the urgent need for effective salvage therapies and early identification of relapse. Currently, relapsed ES is typically managed with various second-line chemotherapy regimens or clinical trials, but responses are often transient, and cure is rare.[15] This reality should temper clinical expectations and motivates exploration of innovative approaches to improve outcomes after recurrence.

Surgical management emerged as a pivotal factor in our cohort, affecting both local disease control and survival. Notably, we observed no significant difference in OS between patients who underwent limb-salvage surgery and those who required amputation, provided that complete tumor resection was achieved. This finding is consistent with the broader orthopedic oncology experience that limb-sparing surgery, when combined with chemotherapy and (if indicated) radiotherapy, can attain equivalent oncologic outcomes to amputation while preserving function.[16] Prior studies in extremity sarcomas have shown that although limb-salvage may carry a slightly higher risk of local recurrence than amputation in some cases, it does not compromise OS as long as clear margins are obtained and effective adjuvant therapy is given.[16] In our series, the use of amputation was reserved for cases where limb-salvage was not feasible (due to neurovascular involvement or extensive disease), or for certain locally recurrent tumors. The fact that survival did not differ by surgical modality underscores that local control – rather than the specific surgical technique – is the key determinant for outcome, allowing most patients to avoid amputation without increasing mortality risk.

Equally important is the comparison of surgical versus non-surgical local therapy. Our results echo the evidence that definitive surgery for the primary tumor is associated with significantly better outcomes in ES. Patients who underwent surgical resection had markedly higher survival than those managed without surgery, reflecting the critical contribution of surgery to durable local control.[11] A surveillance, epidemiology, and end results analysis by Verma et al.[11] similarly demonstrated that resection of the primary tumor conferred a major survival advantage in both pediatric and adult ES patients (5-year OS ~70% with surgery vs ~25% without in that series). The rationale is clear: Uncontrolled primary tumors can be a source of pain, disability, and further metastasis, whereas achieving local tumor clearance improves both quality of life and survival likelihood. In instances where surgery is not possible (e.g., unresectable axial tumors), radiation therapy serves as an alternative for local control, but it is generally less effective than surgery. For example, an analysis of pelvic ES s found that the 5-year local recurrence rate was 22–40% with radiotherapy alone, compared to only ~4–13% with surgical resection (with or without radiation).[16] Our institution's practice of combining surgery with adjuvant radiotherapy for selected cases (such as large pelvic tumors or those with marginal resection margins) is supported by reports that multimodal local therapy can further reduce recurrence risk in challenging anatomic sites.[16] Taken together, our findings reinforce the paradigm that aggressive local control – preferably through surgical resection – is a cornerstone of ES treatment. The type of surgery (limb-salvage vs amputation) can be individualized based on tumor extent and functional

considerations, without adversely impacting survival, as long as complete resection and appropriate adjuvant therapies are achieved. Meanwhile, patients who do not undergo surgery must be monitored closely, as they face higher odds of local failure, which can translate into worse overall outcomes.

Several limitations of this study should be acknowledged when interpreting the results. Most importantly, our analysis is retrospective and from a single institution, which introduces inherent biases in patient selection, treatment approaches, and data completeness. The cohort spanned a wide range of ages (1–78 years) and a long treatment period, during which therapy protocols evolved; thus, heterogeneity in management (pediatric vs adult regimens, older vs newer chemotherapy protocols) could confound the outcomes attributed to age or other factors. Tumor size at diagnosis and surgical margin status were not consistently available across the entire cohort and could not be analyzed, which limits granularity regarding established prognostic factors. Tumor localization was heterogeneous in our cohort, and because the primary site is prognostic and age-dependent in ES, this variability may have confounded age-based comparisons. Being a single-center study, the sample size of certain subgroups (e.g., patients over 40, or those treated with amputation) was relatively small, limiting the statistical power to detect nuanced differences. In addition, unmeasured variables, such as socioeconomic factors, referral patterns, and individual comorbidities in older patients, were not accounted for, yet they may have influenced survival (for instance, some older patients may have received less aggressive therapy due to comorbid conditions). We also lacked granular details on chemotherapy dose intensity and histologic response in all cases, which are known prognostic indicators. Finally, outcomes, such as quality of life and functional status following different surgical treatments, were beyond the scope of this study, but are relevant to patient-centered decision making.

Despite these limitations, our study provides valuable insight into the comparative outcomes across age groups and treatment modalities in ES, a relatively rare cancer. It adds to the growing evidence base that can inform clinical practice. Going forward, multi-center collaborations or prospective registries are warranted to validate our findings in larger, more diverse patient populations. Such studies would help to confirm, for example, whether the survival disparity between adult and pediatric patients persists when care is optimized, and how novel therapies might be altering outcomes over time. Another important future direction is research into the biology of ES across the age spectrum – understanding if there are genomic or tumor microenvironment differences in adult-onset cases could elucidate why older patients fare worse and suggest targeted interventions.

CONCLUSION

In summary, our findings support the continued emphasis on a multidisciplinary, aggressive treatment approach for all ES patients, while also highlighting specific gaps – such as the management of adults and the treatment of metastatic/recurrent disease – where further research and innovative therapies are urgently needed. By addressing these gaps, future studies can build upon the progress to date and hopefully move the needle on survival for those patients who still face a poor prognosis.

DECLARATIONS

Ethics Committee Approval: This study was approved by the Metin Sabanci Baltalimanı Bone Diseases Hospital (Date: 28.10.2024, Decision no: 193).

Informed Consent: All data were obtained from existing medical records, with patient confidentiality preserved.

Conflict of Interest: None declared.

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LETTER TO THE EDITOR

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Paracetamol Use and Alleged Association with Autism Spectrum Disorder

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Dear Editor,

Recent public discussions have raised concerns regarding a purported association between paracetamol (acetaminophen) use – particularly during pregnancy – and the subsequent development of autism spectrum disorder (ASD) in children. While these claims have been amplified by media and public figures, current scientific evidence does not support a causal relationship between paracetamol exposure and ASD.

Paracetamol has been used safely for over 50 years as one of the most widely recommended analgesic and antipyretic agents in pediatric and obstetric practice. Although some observational studies suggest a possible association between prenatal paracetamol exposure and neurodevelopmental outcomes, these studies are heavily limited by confounding factors such as maternal fever, viral infections, genetic predisposition, recall bias, and difficulties in accurately estimating dosage and timing. Notably, fever itself is an established risk factor for adverse neurodevelopmental outcomes, making it difficult to distinguish the effects of fever from the effects of the medication used to treat it.

Importantly, no randomized controlled trials or well-designed prospective cohort studies have demonstrated a direct causal link between paracetamol use and ASD. Furthermore, no plausible biological mechanism has been identified that would support such a claim. Several recent meta-analyses and expert committee evaluations have concluded that available data are insufficient to recommend limiting clinically indicated paracetamol use during pregnancy or childhood.[1-18]

Dissemination of unsupported claims regarding medication safety may lead to treatment hesitancy among parents, potentially resulting in undertreatment of fever or pain, which carries its own well-documented risks. Public health communication must rely on robust, high-quality evidence to prevent unnecessary anxiety and avoid detrimental health outcomes.

Existing scientific literature does not support a causal relationship between paracetamol use and ASD. Paracetamol remains a safe, effective, and essential therapeutic option when used appropriately. Claims suggesting otherwise should be interpreted with caution and in the context of well-established scientific evidence.

DECLARATIONS

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