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The Effect of Bone Marrow CD4/CD8 Ratio on Lymphoma Response and Survival: Single Center Experience

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ABSTRACT

Introduction: A minor subset of CD4+ T cells, known as regulatory T cells (Tregs), makes up 1-4% of lymphocytes in circulation. These cells are responsible for regulating excessive immune responses, promoting immune tolerance, and suppressing anti-tumor immunity. This study aimed to investigate how the CD4/CD8 ratio influences treatment outcomes and survival rates in patients newly diagnosed with lymphoma. The research involved analyzing samples extracted from bone marrow aspirates.

Methods: Our study included individuals diagnosed with lymphoma at the Clinic of Hematology in University of Health Sciences Türkiye, İstanbul Training and Research Hospital from January 2010 to January 2021. These patients underwent flow cytometric analysis of bone marrow aspiration samples at the time of their initial diagnosis.

Results: In the statistical analysis performed to reveal the effect of CD4/CD8 ratio on the interim response to treatment, the ratio was found to be significantly higher in patients with a response of complete response "(CR)" compared to others (p=0.003). The statistical analysis performed to reveal the effect of the ratio on the end-of-treatment response found higher in patients with a CR response compared to others (p=0.008). CD4/CD8 ratio did not have a significant effect on survival.

Conclusion: According to the literature review, the increase in the ratio of non-Treg CD4+ cells, and the high CD4/CD8 ratio contributes positively to the response. It will shed light on new studies evaluating the effect of subtypes of CD4+ T cells on response and survival in lymphomas.

Keywords: Lymphoma, CD4+ T cells, CD4/CD8 ratio, response, survival

Introduction

T lymphocytes can be categorized into two main groups: CD4+ helper T cells and CD8+ cytotoxic T cells. CD4+ T cells identify antigenic epitopes displayed by major histocompatibility complex (MHC) II molecules and undergo differentiation upon antigenic stimulation (1). In contrast, CD8+ T cells recognize antigens presented on MHC class I molecules and transform into cytotoxic CD8+ T cells when activated. Although CD8+ Tregs produce various cytokines, their primary function is to eliminate infected host cells. The activation of CD8+ T cells requires mediator stimuli, which can occur with or without CD4+ T cells involvement (1-4).

A small subset of CD4+ T cells, known as regulatory T cells (Tregs), comprises 1-4% of circulating lymphocytes (1). These cells play a crucial role in regulating excessive immune activity and promoting immune tolerance (3). Tregs are characterized by their expression of surface interleukin 2 receptors and are identified by CD25 and FOXP3+ (3,4). They have been shown to promote tumor progression and suppress antitumoral immune responses (5,6) and negatively impact survival rates (6-10). Despite the potential anti-cancer effects of CD4+ T lymphocytes through the activation of CD8+ cytotoxic T lymphocytes, evidence suggests that the current increased CD4+ T cell ratio has a detrimental role in cancer pathogenesis and adversely affects treatment response and survival.

The role of the CD4/CD8 ratio in hematological malignancies differs significantly from that in solid tumors, making it a relatively new area of research for prospective studies. This study aims to investigate the impact of the CD4/CD8 ratio on treatment response and survival in newly diagnosed lymphoma patients by analyzing bone marrow aspirate samples.

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Methods

Our study included patients diagnosed with lymphoma at the Clinic of Hematology, University of Health Sciences Türkiye, İstanbul Training and Research Hospital from January 2010 to January 2021, whose bone marrow aspirations underwent flow cytometric analysis at diagnosis. We collected data on patient demographics (age and gender at diagnosis), lymphoma subtypes, initial staging, bone marrow involvement status based on pathological evaluation, initial laboratory values (leukocyte counts, neutrophil counts, lymphocyte counts, hemoglobin counts, platelet counts), bone marrow CD4/CD8 ratios, treatment responses, and survival outcomes. Treatment response was evaluated at two points: interim and end-of-treatment, using the Lugano criteria (11).

We excluded patients with Tregs lymphoma and bone marrow involvement due to potential effects on the bone marrow CD4/CD8 ratio. Furthermore, we omitted patients lacking initial evaluation, bone marrow samples, or continued follow-up or treatment in our department. Those whose treatment response could not be assessed for any reason were also excluded from the study.

Samples and Analysis

Patients' bone marrow samples were collected in EDTA tubes and examined within 2 hours using the XN 9000 (Sysmex, Kobe, Japan). A 3-laser, 10-color FACSLyric flow cytometry analyzer (BD Biosciences, San Jose, United States of America) was utilized for flow-cytometric analysis. Prior to running samples, calibration controls and compensation adjustments were conducted. The system's performance was verified using standardized beads. EDTA-containing samples were maintained at room temperature and analyzed within 24 hours. The antibodies employed were CD4 V450 (SK3 clone) and CD8 FITC (SK1 clone). Analysis was carried out using BD FACSSUITE software. The research was reviewed and approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (approval number: 2573, date: 13.11.2020) and was conducted according to the principles of the Declaration of Helsinki.

Statistical Analysis

In the data analysis, descriptive statistics for continuous variables included the mean, standard deviation, and range (minimum and maximum values). Categorical variables were described using frequencies and percentages. To compare means between two independent groups, Student's t-test and the Mann-Whitney U test were utilized. The relationship between categorical variables was assessed using chi-square or Fisher's Exact test statistics. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to identify differences based on risk factors. Hazard ratios were reported with 95% confidence intervals (CI). To determine optimal cut-off values, the receiver operating characteristic (ROC), area under the curve (AUC) was calculated, with significance evaluated through sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio statistics. ROC curves were plotted to quantify the AUCs with 95% CI. The AUC values were categorized as follows: 0.90-1 (excellent), 0.80-0.90 (good), 0.70-0.80 (fair), 0.60-0.70 (low), and 0.50-0.60 (fail). Statistical significance was set at $p<0.05$. Data analysis was conducted using IBM SPSS version 25 and MedCalc statistical software.

Results

A total of 126 patients were included in the study. 79.4% of the patients were diagnosed with B cell lymphoma (n=100), 8.7% with T cell l lymphoma (n=11), and 11.9% with Hodgkin lymphoma (HL). The mean age was 52.1±15.9 years (range: 19-88). The number of patients with stage 4 disease at the time of diagnosis was 56 (44.4%). The number of patients with bone marrow involvement was 47 (n=37.3%). The number of patients with complete response (CR) in the interim evaluation was 47 (37.7%) and with CR + partial response (PR) was 104 (82.5%). At the end-of-treatment evaluation, the number of patients with a CR was 57 patients (45.2%), and with (CR + PR) was 102 patients (81%) (Table 1).

Flow cytometric analysis revealed a mean CD4/CD8 ratio of 1.08±1.01 at diagnosis. Statistical evaluation of the ratio's impact on interim treatment response showed a significantly higher value in patients achieving CR compared to others (p=0.003). The mean ratio was 1.48±1.16 in CR patients and 0.85±0.67 in non-CR patients. No significant differences

Table 1. Descriptive statistics of socio-demographic characteristics, clinical and laboratory data

		$\bar{x} \pm SD$	Min.-Max.
Age		52.1±15.9	19-88
		n	%
Gender	Female	45	35.7
	Male	81	64.3
Lymphoma subtypes	Hodgkin	15	11.9
	B-cell	100	79.4
	T-cell	11	8.7
Stage at the time of diagnosis	1	12	9.5
	2	19	15.1
	3	39	31
	4	56	44.4
Bone marrow involvement	(-)	79	62.7
	(+)	47	37.3
Progression	(-)	94	74.6
	(+)	32	25.4
Interim response	CR	47	37.3
	Others	79	62.7
Interim response	CR + PR	104	82.5
	Others	22	17.5
End-of-the-treatment response	CR	57	45.2
	Others	69	54.8
End-of-the-treatment response	CR + PR	102	81
	Others	24	19
Mortality	Alive	93	73.8
	Exitus	33	26.2
CD4/CD8		1.08±1.01	0.11-5.1

SD: Standard deviation, CR: Complete response, PR: Partial response, Min.: Minimum, Max.: Maximum

were observed when grouping patients as CR + PR compared to others, with p=0.17 (Table 2).

Analysis of the ratio's effect on end-of-treatment response indicated higher values in CR patients compared to others (p=0.008). CR patients had a mean ratio of 1.36±1.02, while others had 0.86±0.71. The mean CD4/CD8 ratio was notably higher in patients with CR + PR compared to others (p<0.001) (1.19±1.01 and 0.65±0.38, respectively) (Table 2).

Regarding the ratio's effect on interim response, cut-off values for CD4/CD8 did not yield significant results. Neither statistical analysis of CR nor CR + PR treatment response groups yielded significant outcomes (p>0.05) (Table 3, Graphics 1, 2).

The statistical analysis of end-treatment response revealed significant findings. For the 0.38 cut-off value indicating end-of-treatment unresponsiveness (excluding CR), sensitivity was 35.29% and specificity was 89.47%. The positive predictive value reached 80%, while the negative predictive value was 53.7% (95% CI: 0.56-0.73, AUC: 0.65, p=0.002). Regarding the 0.87 cut-off value for CR + PR response, sensitivity and specificity were 79.17% and 54.46%, respectively. The positive predictive value was 29.2%, and the negative predictive value was 91.7% (95% CI: 0.59-0.76, AUC: 0.68, p=0.004) (Table 3, Graphics 3, 4).

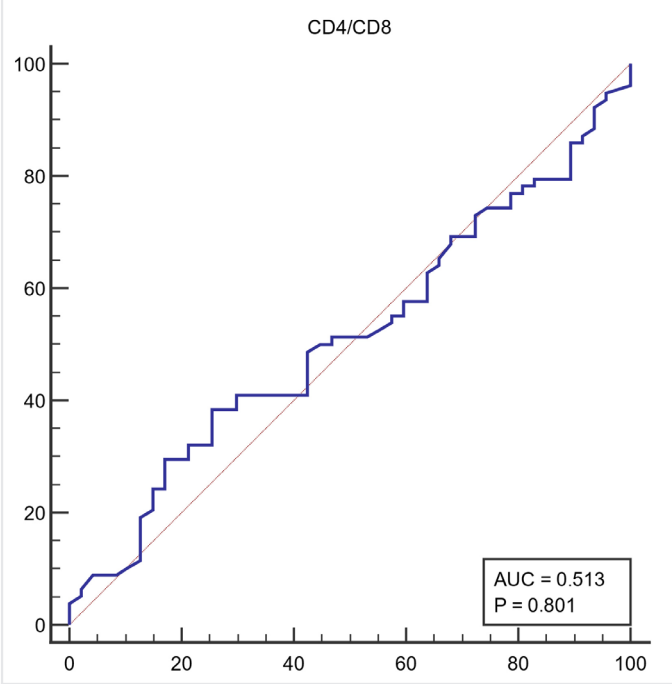
Table 2. The effect of CD4/CD8 ratio on the interim and end-of-treatment response

		$\bar{x} \pm SD$	p-value
Interim response	CR	1.48±1.16	**0.003**
	Others	0.85±0.67	
	CR + PR	1.15±1.01	0.17
	Others	0.82±0.73	
End-of-treatment response	CR	1.36±1.02	**0.008**
	Others	0.86±0.71	
	CR + PR	1.19±1.01	**<0.001**
	Others	0.65±0.38	

(p<0.05 significance), Student's t-test, SD: Standard deviation, CR: Complete response, PR: Partial response

During the 0-90 month period, 33 patients (26.9%) died. Among those with a CD4/CD8 ratio ≤0.87, 18 (27.7%) died, while 48 (72.73%) survived. Analysis of overall survival (OS) revealed no significant difference in survival curves, indicating that the CD4/CD8 ratio did not significantly impact mortality (p>0.05) (Table 4 and Graphic 5).

Disease progression occurred in 32 patients (25.4%) within the 0-90 month timeframe. For patients with a CD4/CD8 ratio ≤0.87, 22 (33.3%) experienced progression, while 44 (66.7%) did not. In the group with a CD4/CD8 ratio >0.87, 10 patients (16.67%) progressed, and 50 (83.33%) remained progression-free. The CD4/CD8 ratio showed no significant effect on progression-free survival (PFS) (p>0.05) (Table 4 and Graphic 6).



Graphic 1. Interim evaluation: patients with a response of CR and others
CR: Complete response, AUC: Area under the curve

Table 3. Evaluation of the diagnostic accuracy of CD4/CD8 ratio in distinguishing treatment response

	AUC	Cut-off	Sensitivity %	Specificity %	AUC 95% CI	p	PPV %	NPV %
Interim evaluation								
No response: 78 Response (CR): 47	0.51	≤0.52	38.46	74.47	0.42-0.61	0.81	71.4	42.2
No response: 22 Response (CR + PR): 103	0.52	>2.03	22.73	91.26	0.43-0.61	0.76	35.7	84.7
End-of-treatment								
No response: 68 Response (CR): 57	0.65	≤0.38	35.29	89.47	0.56-0.73	**0.002**	80	53.7
No response: 24 Response (CR + PR): 101	**0.68**	≤0.87	79.17	54.46	0.59-0.76	**0.004**	29.2	91.7

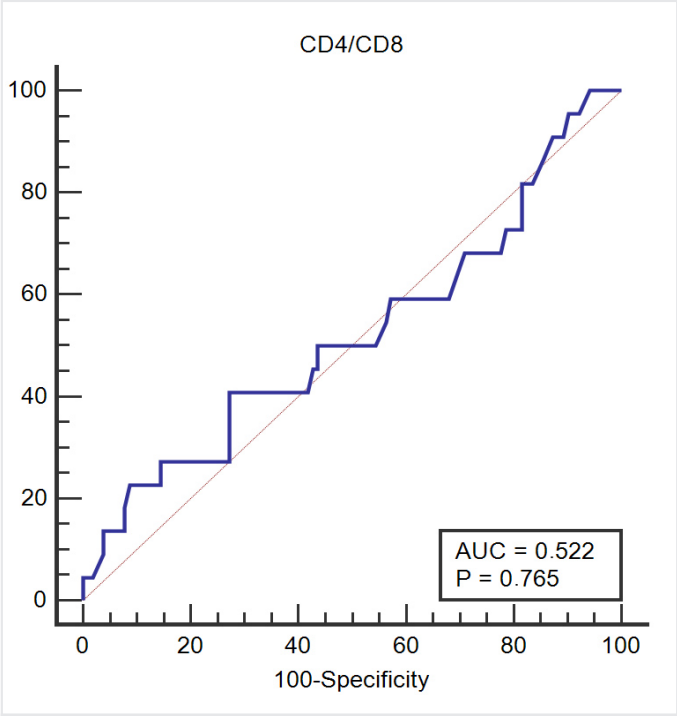
CR: Complete response, PR: Partial response, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

Discussion

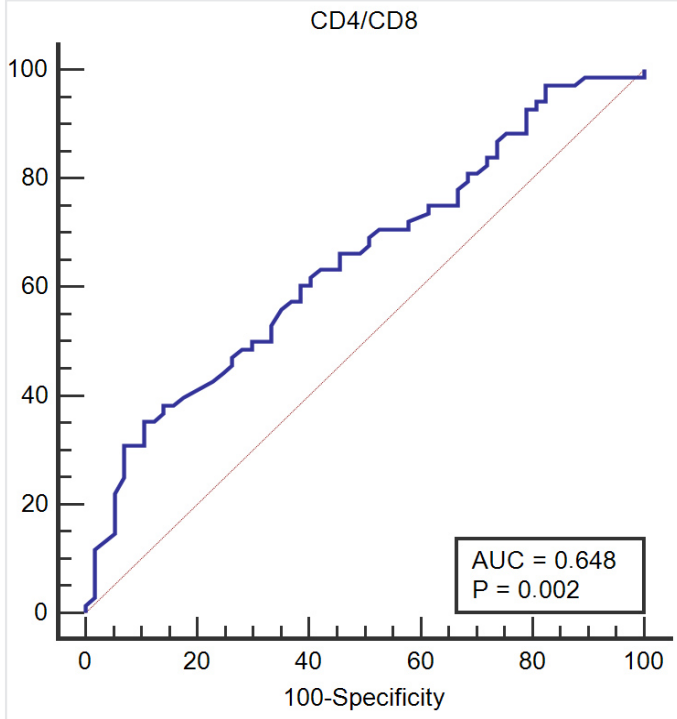
Our research revealed that the CD4/CD8 ratio had a significant impact on treatment responses. For the interim response, patients achieving CR showed a notably higher rate compared to other response groups. Similarly, for the end-of-treatment response, the ratio was elevated in CR patients relative to others. Additionally, patients with either CR or PR demonstrated a significantly higher mean CD4/CD8 ratio than those with other outcomes. Analysis of end-of-treatment response indicated that a CD4/CD8 ratio cut-off of 0.38 for non-CR responses yielded 35.29% sensitivity and 89.47% specificity. For CR + PR responses, a cut-off value of 0.87 provided 79.17% sensitivity and 54.46% specificity. However, the CD4/CD8 ratio did not significantly influence patient survival.

Although literature data evaluating lymphoma and the CD4/CD8 ratio is quite limited, the role of the ratio in different hematological malignancies has been evaluated and analyses have been presented. Generally, the increase in CD4+ cells and the "Tregs" among them had a negative effect on the treatment of malignancy due to the immunosuppressive effects; however, in our study, it was revealed that the increase in the ratio was found to be associated with a treatment response of CR in lymphomas. Our results may seem different from the literature when evaluated over the ratio; they are actually aligned with the literature data.

There are very few studies examining CD4+, CD8+, and other Tregs distributions, especially in bone marrow aspiration materials. In one of them, Braga et al. (12) evaluated Tregs in bone marrow aspirates of a total of 46 patients diagnosed with multiple myeloma (MM), 4 patients with monoclonal gammopathy of undetermined significance, and solitary plasmacytoma. When compared to the healthy controls, it



Graphic 2. Interim evaluation: Patients with a response of CR + PR and others
CR: Complete response, PR: Partial response, AUC: Area under the curve



Graphic 3. End-of-treatment evaluation: patients with a response of CR and others
CR: Complete response, AUC: Area under the curve

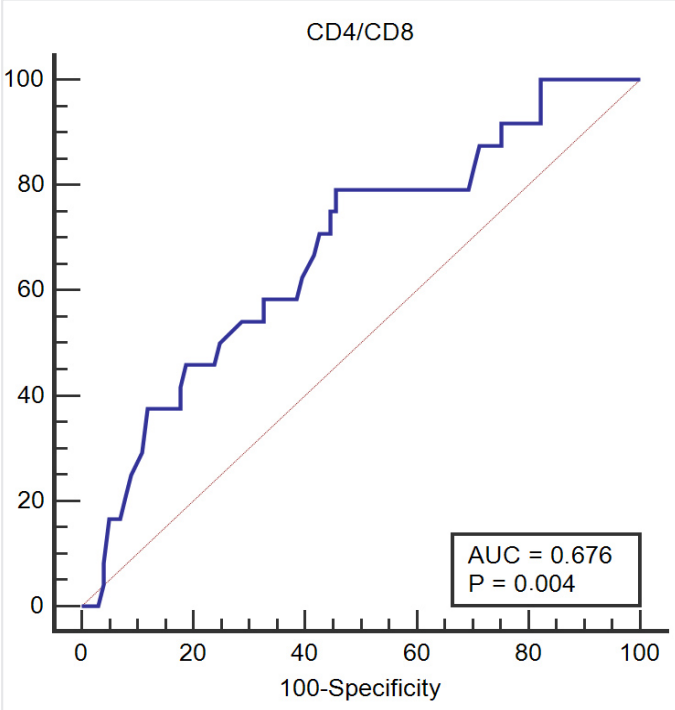
Table 4. Survival analyses: Overall survival and progression-free survival

CD4/CD8	Exitus n (%)	Non-exitus n (%)	Median survival (95% CI)	Hazard ratio (95% CI)	Log rank p-value
≤0.87 (n=66)	18 (27.27)	48 (72.73)	61 (32-64)	1.001 (0.49-2.03)	0.98
>0.87 (n=60)	15 (25)	45 (75)	71 (30-79)		
Total	33 (26.19)	93 (73.81)	64 (49-79)		
	Progressed n (%)	Non-progressed n (%)			
≤0.87 (n=66)	22 (33.3)	44 (66.7)	34 (24-53)	1.81 (0.89-3.68)	0.09
>0.87 (n=60)	10 (16.67)	50 (83.33)	66 (54-78)		
Total	32 (25.4)	94 (74.6)	70 (31-70)		

CI: Confidence interval

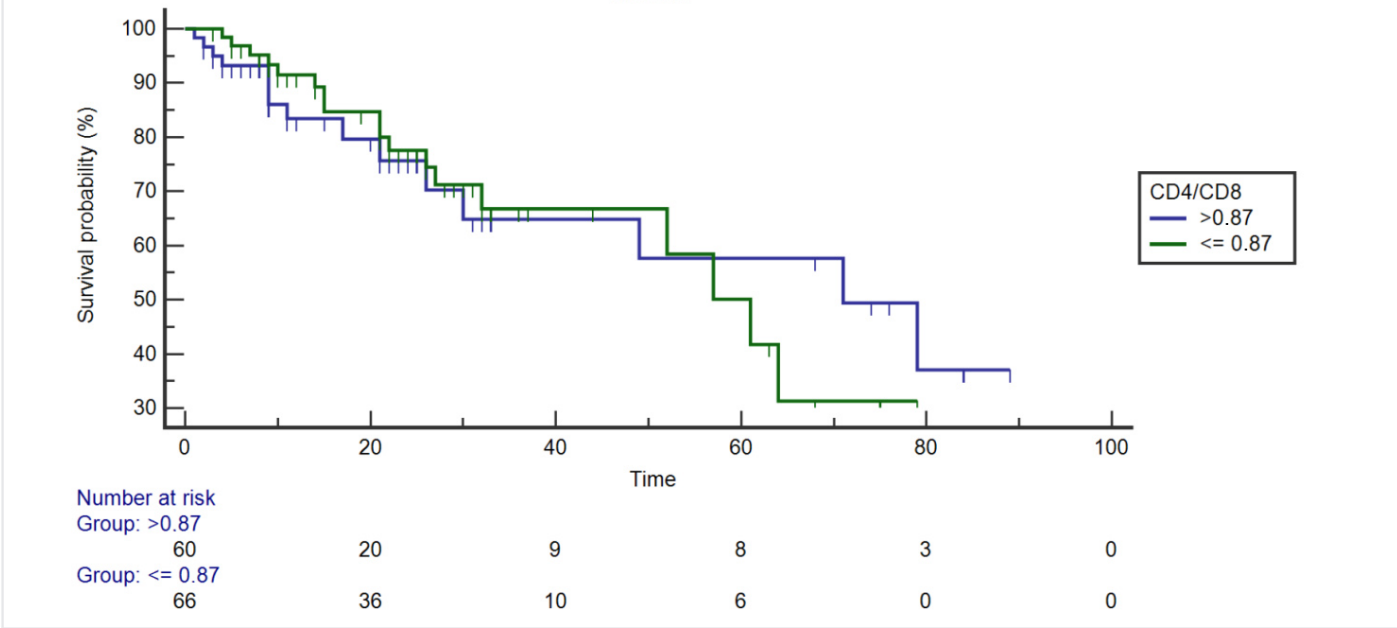
was observed that the FOXP3+ group was 30 times higher in patients diagnosed with MM. Based on that, it has been suggested that immune dysregulation may play a role in the pathogenesis of MM.

A lymph node study investigating the proportion of FOXP3+ cells (13) revealed that an increased number of these cells correlated with improved PFS in follicular lymphoma and diffuse large B-cell lymphoma (DLBCL), as well as better OS in HL and germinal-center DLBCL. However, it was associated with poorer OS in non-germinal DLBCL. Another investigation focused on CD4+ and CD25+ cell percentages in DLBCL lymph node biopsies, finding that higher levels of these cells were linked to worse survival outcomes and International Prognostic Index scores (14). Additionally, a separate lymph node analysis of relapsed/refractory HL patients showed that low regulatory Treg levels were connected to reduced OS (15). These investigations concentrate on affected lymph nodes, or "tumor tissue," and varying results may occur due to potential differences in disease mechanisms. Conversely, examining bone marrow aspirates, which may indicate systemic immune responses, can yield distinct findings, as observed in our research when compared to existing literature. While no significant survival correlations were found, the ratio proved influential in both interim and end-of-treatment responses. The response improves as the ratio increases, a finding not previously reported in the literature.

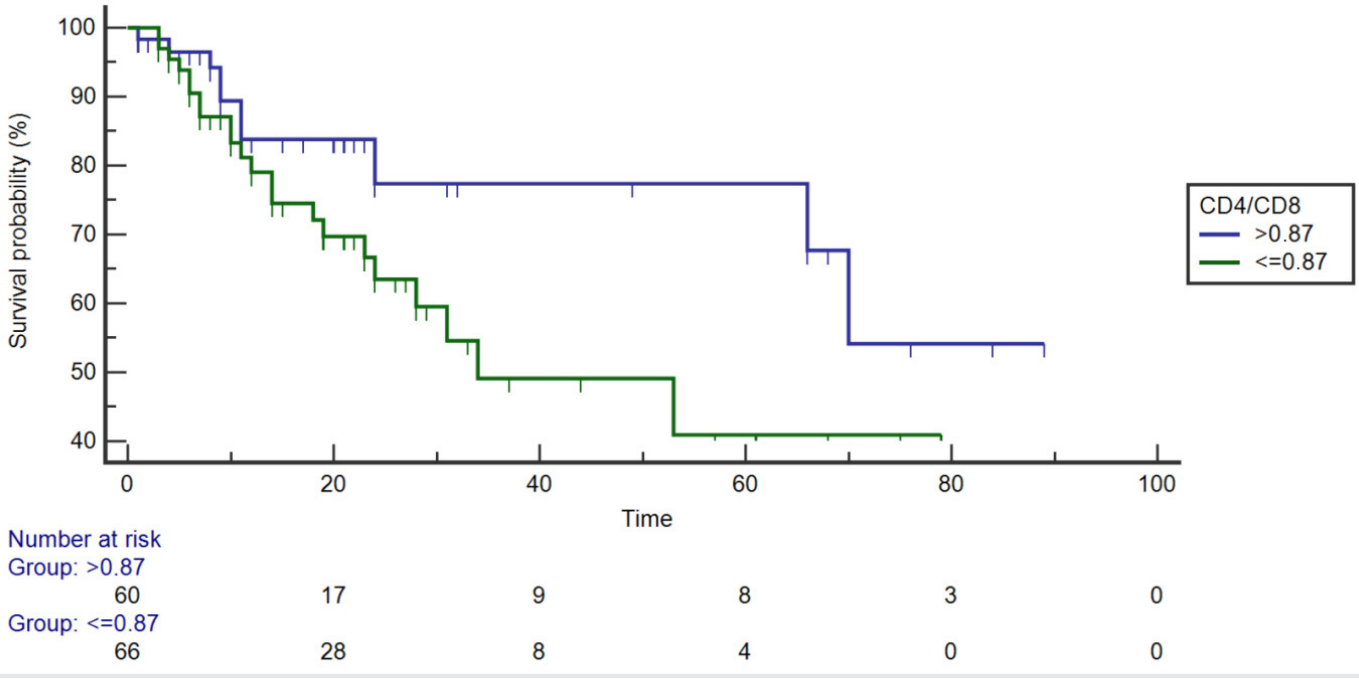


Graphic 4. End-of-treatment evaluation: patients with a response of CR + PR and others
CR: Complete response, PR: Partial response, AUC: Area under the curve

In another study (16), researchers performed bone marrow sampling and evaluated the effect of subtyping on response and survival. Patients diagnosed with B-acute lymphoblastic leukemia were examined, and an increase in Treg was found to be associated with disease progression. Another study (17) evaluated 39 patients with acute lymphoblastic leukemia (ALL). The high CD4/CD8 ratio in bone marrow aspirates taken before treatment with the pediatric ALL regimen showed a positive correlation with the 15th day response. When the CD4+ cell subgroups were evaluated separately, non-Treg cells were found to be higher compared to others, excluding CD4+, CD25+, FOXP3+ Treg cells. Therefore, the interpretation is that the increase in the ratio of non-Treg CD4+ cells and the high CD4/CD8 ratio contributes positively to the response. We think that a similar mechanism was effective in our study; however, the fact that subtyping could not be studied was an important limitation.



Graphic 5. Overall survival probabilities (%)



Graphic 6. Progression-free survival probabilities (%)

Study Limitations

There were important additional limitations of our study. Subtyping of CD4+ cells could not be studied in our flow cytometry laboratory. For this reason, subtyping could not be performed. In another study, the evaluation of CD25+, FOXP3+ cells using appropriate subtyping methods will be much more accurate. Another important limitation was the restricted patient population, as it included single-center data.

Conclusion

In conclusion, in our study, the CD4/CD8 ratio was found to be significantly higher in patients with a CR response compared to others, in terms of the interim response to treatment. In the statistical analysis performed to reveal the effect of the ratio on the end-of-treatment response, it was found to be higher in patients with response of CR, compared to others. The CD4/CD8 ratio did not have a significant effect on OS and PFS. It was revealed that the ratio was effective both in the interim and at the end-of-treatment response. The response increases as the ratio increases. It will shed light on new studies evaluating the effect of subtypes of CD4+ Tregs on response and survival in lymphomas.

Ethics

Ethics Committee Approval: The research was reviewed and approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (approval number: 2573, date: 13.11.2020) and was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Prospective studies.

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Footnotes

Authorship Contributions: Concept - D.S., B.O., H.S., O.Y.; Design - D.S., B.O., H.S., O.Y.; Data Collection or Processing - V.C.Ç., İ.S.; Analysis or Interpretation - V.C.Ç., İ.S.; Literature Search - V.C.Ç., İ.S.; Writing - V.C.Ç., İ.S.

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Preoperative Calcium-Phosphorus Status and Arteriovenous Fistula Maturation

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ABSTRACT

Introduction: Although arteriovenous fistula (AVF) is the preferred vascular access in hemodialysis (HD) practice, AVF maturation is a common issue. The current study investigated the possible role of preoperative serum calcium/phosphate levels in predicting AVF maturation.

Methods: Only patients with end-stage kidney disease who were candidates for chronic HD were included. The key inclusion criterion was having a newly created radiocephalic AVF. Patients who started chronic HD before AVF operation were excluded. A mature AVF was defined as blood flow >500 mL/minute and an access (cephalic) vein diameter >5 mm at 6 to 8 weeks post-operation, in ultrasonography.

Results: A total of 79 patients were included, with a median age of 62.4 years. AVF maturation was identified in 50 patients (63.3%). Serum calcium level was 8.9±0.6 mg/dL in patients with mature AVF and 8.6±0.5 mg/dL in patients with immature AVF (p=0.03). Hypocalcemia was more frequent (31.0% compared to 16%) in patients with immature AVF, whereas it was not statistically significant (p=0.117). A positive correlation was identified between serum calcium levels and cephalic vein diameters (p=0.012). Serum phosphate, parathyroid hormone, and calcium phosphate product were not significantly different between the two groups. Logistic regression analysis revealed that serum calcium level was an independent predictor for AVF maturation (p=0.035). In receiver operating characteristic analysis, sensitivity and specificity of calcium level (cut-off >8.7 mg/dL) were 70.0% and 59.6%, respectively, with an area under the curve of 0.65 (95% confidence interval 52.4-77.6, p=0.027).

Conclusion: Understanding the impact of preoperative calcium levels on AVF maturation may guide clinicians in optimizing biochemical parameters preoperatively, thus enhancing fistula success rates.

Keywords: Arteriovenous fistula, maturation, calcium, hypocalcemia, hemodialysis

Introduction

In chronic hemodialysis (HD) practice, arteriovenous fistula (AVF) is the preferred vascular access option. A mature AVF should have several features such as sufficient blood flow, a straight and adequate segment for cannulation, and be able to be cannulated repeatedly. Unfortunately, even with a successful operation, maturation presents a challenge for AVF utilization. Inadequate dilatation and early stenosis are among the frequent causes of AVF maturation failure (1). Clinicians should identify which potential risk factors are most relevant to fistula development in patients awaiting vascular access creation (2).

In normal physiological conditions, parathyroid hormone (PTH) stimulates osteoclast activity, resulting in the resorption of calcium and phosphorus from the bone. PTH also promotes the activation of vitamin D in the kidneys. Active vitamin D enhances the absorption of calcium and phosphorus from the gastrointestinal tract and kidney tubules (3). However, calcium and bone metabolism are impaired in chronic kidney disease (CKD). Increased PTH and phosphate levels, with decreased calcium levels, are the main laboratory findings.

CKD-mineral and bone disorder (MBD) is a broad term for these disturbances and is not limited to secondary hyperparathyroidism. Phosphate retention, along with decreased glomerular filtration, essentially triggers this pathological process (4). The underlying mechanisms of CKD-MBD are complicated, involving intricate feedback loops between the kidneys, parathyroid glands, bones, intestines, and vasculature (5). The current study examined the AVF maturation problem, regarding calcium-phosphorus metabolism parameters.

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Methods

This clinical investigation was carried out in accordance with the Helsinki Declaration. The procedure of the study was explained to the patients to obtain written informed consent. This study was conducted as a single-center, observational study. This study has been approved by the Erciyes University Health Sciences Research Ethics Committee (approval number: 2024/269, date: 04.12.2024).

Study Design

This retrospective study was conducted in a single center. The patient screening period was limited to two years from 01/2023 to 12/2024. The key inclusion criterion was having a newly created AVF for chronic HD treatment and subsequently being assessed by ultrasonography (USG) for AVF maturation. Only adult patients with radiocephalic fistula were enrolled. Patients undergoing chronic HD before AVF operation were excluded. Patients with an AVF that was non-functioning shortly after the operation were excluded. Also, patients were not excluded if a dialysis catheter was concurrently inserted during the operation due to immediate HD indications.

Arteriovenous Fistula Maturation Assessment

Maturation was identified by USG at 6-8 weeks after the AVF operation. The access vessel (cephalic vein) diameter, the feeding artery (radial artery) diameter, and the fistula blood flow rate (5 cm proximal to the anastomosis) were measured by Duplex USG. A mature AVF was defined as a cephalic vein diameter >5 mm and a fistula blood flow >500 mL/minute (min).

Laboratory Assessment

Preoperative laboratory results were used in analyses. Total serum calcium measurement was corrected according to the serum albumin. Corrected calcium (mg/dL) was calculated using the following formula. Measured total calcium (mg/dL) + 0.8 x [4.0 - serum albumin (g/dL)]. Hypocalcemia was defined as a total serum calcium concentration below 8.5 mg/dL, and hyperphosphatemia was defined as a serum phosphate concentration above 4.5 mg/dL.

Statistical Analysis

Histograms and q-q plots were examined, and the Shapiro-Wilk test was performed to assess the normality of the data. Levene's test was applied to test variance homogeneity. To compare the differences between groups, either a two-sided Independent samples t-test or Mann-Whitney U test was used for continuous variables, or Pearson's $\chi 2$ analysis or Fisher's exact test was used for categorical variables. The Spearman correlation coefficient was used to explore the relationship between numerical variables. Binary logistic regression analyses were performed to identify the risk factors for progression. Predicted probabilities of each model were included in receiver operating characteristic (ROC) curve analysis to identify and compare the predictive performances of the models. Analysis was conducted using R 4.2.3 (http://www.r-project.org) and EasyROC software. A p-value less than 5% was considered statistically significant.

Results

In this study, a total of 79 patients were analyzed. The mean age of patients was 62.4±11.8 years. Sixty-nine patients (87.3%) underwent only an AVF creation as a first HD access. Dialysis catheter insertion concurrently with AVF creation was performed in 10 patients (12.7%, 12.7) due to urgent dialysis indications.

Diabetes mellitus (DM) was diagnosed in 29 patients (36.7%) and was the most common primary cause of CKD in our cohort. Hypertension (HT) ranked as the second most prevalent primary cause of CKD (26.6%), although HT was diagnosed in 55 patients (69.6%). Peripheral vascular disease (PVD) was identified in 5 patients (6.3%) as a comorbidity.

Mature AVF was identified in 50 patients (63.3%). The median fistula blood flow was 685.0 (622.0-750.0) mL/min in patients with mature AVF and 180.0 (130.0-250.0) mL/min in patients with non-maturing AVF. The mean access vessel (cephalic vein) diameter was 5.2 (4.6-5.7) mm in patients with mature AVF, and 2.8 (1.7-3.6) mm in patients with non-maturing AVF. The median radial artery diameter was 4.1 (3.6-4.6) mm in patients with mature AVF, and 2.3 (2.0-3.0) mm in patients with non-maturing AVF.

The mean age was 59.4±12.1 in patients with mature AVF and 67.5±9.5 in patients with non-maturing AVF. Also, age was statistically significantly higher in patients with non-maturing AVF (p=0.002). Laboratory parameters were analyzed according to AVF maturation groups. There were no statistically significant differences in blood urea nitrogen, creatinine, sodium, potassium, uric acid, protein, albumin, aspartate aminotransferase, alanine aminotransferase, leukocyte, or hemoglobin levels between the two groups. The results are summarized in Table 1.

Two AVF maturation groups were analyzed according to the presence of DM. AVF immaturity rate was 58.6% in diabetic patients, whereas it was 24.0% in non-diabetic patients. The frequency of non-maturing AVF was statistically significantly higher in diabetic patients (p=0.002).

Two AVF maturation groups were analyzed according to the presence of HT. AVF maturation rate was 60.0% in hypertensive patients, whereas it was 70.8% in non-hypertensive patients. The frequency of maturing AVF was not significantly higher in diabetic patients (p=0.255).

Only four patients used calcium-containing phosphate binders, so we did not analyze these patients based on AVF maturation status. Additionally, 20 patients (25.3%) used oral calcitriol (active vitamin D) medication. No association was found between AVF maturation and whether patients used calcitriol (p=0.124).

The average total serum calcium level was 8.8±0.6 mg/dL in all patients, and the hypocalcemia frequency was 21.5% (n=17). Serum total calcium level was statistically significantly higher in patients with mature AVF (8.9±0.6 mg/dL) than in those with non-maturing AVF (8.6±0.5 mg/dL). The results are summarized in Table 2.

The frequency of hypocalcemia was 16.0% (n=8) in patients with mature AVF, and 31.0% (n=9) in patients with non-maturing AVF. Despite the higher frequency of hypocalcemia in patients with non-maturing AVF, it was not statistically significant (p=0.117).

The average serum phosphate level was 4.1±1.0 mg/dL in all patients, with hyperphosphatemia occurring in 29.1% (n=23). Serum phosphate level was 4.1±1.1 mg/dL in patients with mature AVF, 4.2±0.8 mg/dL in patients with non-maturing AVF, and a statistically significant difference was not determined (p=0.364). The frequency of hyperphosphatemia was 30.0% (n=15) in patients with mature AVF and 27.6% (n=8) in patients with non-maturing AVF. Despite the higher frequency of hyperphosphatemia in patients with mature AVF, it was not statistically significant (p=0.820).

The average calcium phosphate product (CaxP) value was 35.9±11.1 mg^2/dL^2 in patients with mature AVF, and 36.9±8.5 mg^2/dL^2 in patients with non-maturing AVF. There was no statistically significant difference in CaxP values between the two AVF maturation groups (p=0.684).

The median PTH level was 207 (93.5-281.5) pg/mL in patients with mature AVF, and 242 (93.5-281.5) pg/mL in patients with non-maturing AVF. There was no statistically significant difference in serum PTH levels between the two AVF maturation groups (p=0.655).

No correlation was identified between serum calcium levels and fistula blood flows (p=0.123), as shown in Figure 1. However, a positive correlation was identified between serum calcium levels and cephalic vein diameters (p=0.012), as shown in Figure 2. Serum phosphate levels were not correlated with fistula blood flows (p=0.878) and cephalic vein diameters (p=0.343). CaxP values and PTH levels were not correlated with fistula blood flows or cephalic vein diameters.

Binary logistic regression analysis identified two independent predictors of AVF maturation: serum calcium level (p=0.035) and age (p=0.006). The results are summarized in Table 2.

Serum calcium levels significantly predicted AVF maturation in ROC analysis. The sensitivity and specificity of calcium level were 70.0% and 59.6% (cut-off >8.7 mg/dL) with an area under the ROC curve of 0.65, (95% confidence interval 52.4-77.6, p=0.027). The results are summarized in Table 3, and the ROC diagram is shown in Figure 3.

Table 1. Comparison of the patients according to AVF maturation status

Parameters	Mature AVF (n=50)	Immature AVF (n=29)	p
Age (years)	59.4±12.1	67.5±9.5	0.002
BMI (kg/m^2)	24.4 (22.4-28.4)	25.5 (22.4-29.3)	0.855
Glucose (mg/dL)	108 (93-167)	120 (102-166)	0.234
BUN (mg/dL)	41 (37-64)	48 (29-45)	0.134
Creatinine (mg/dL)	4.7 (3.6-6.1)	3.7 (3.3-5.1)	0.085
Uric acid (mg/dL)	5.7±1.8	5.7±2.1	0.994
Sodium (mmol/L)	137.8±3.7	137.9±2.4	0.832
Potassium (mmol/L)	4.3 (4.1-5.0)	4.4 (4.0-5.0)	0.780
Protein (g/dL)	6.4±0.7	6.7±0.8	0.166
Albumin (g/dL)	3.8 (3.4-4.2)	3.8 (3.2-4.0)	0.684
Calcium (mg/dL)	8.94±0.63	8.62±0.58	**0.030**
Phosphate (mg/dL)	4.11±1.12	4.20±0.85	0.364
CaxP (mg^2/dL^2)	35.9±11.1	36.9±8.5	0.684
PTH (pg/mL)	207 (93.5-281.5)	242 (93.5-281.5)	0.655
Hemoglobin (g/dL)	10.6±1.7	10.5±1.7	0.679
Leukocyte (cell/µL)	7.4±2.4	8.2±2.3	0.163
Platelet (10^3/µL)	222 (192-275)	213 (171-309)	0.383

Values are expressed as mean ± standard deviation, median (1^{st}-3^{rd} quartiles), AVF: Arteriovenous fistula, BUN: Blood urea nitrogen, BMI: Body mass index, CaxP: Calcium phosphate product, PTH: Parathyroid hormone

Table 2. The results of binary logistic regression analysis

Parameters	β	HR	95% CI	p
Age	-0.077	0.926	0.878-0.977	**0.005***
BUN	0.330	1,033	0.993-1,075	0.106
Creatinine	0.049	1,051	0.781-1,413	0.745
Protein	0.377	1,459	0.428-4,970	0.546
Glucose	-0.002	0.998	0.989-1,006	0.605
Calcium	0.927	2,528	1,069-5,977	**0.035***
Phosphate	-0.457	0.633	0.055-7,359	0.715
CaxP	0.005	1,005	0.755-1,337	0.937
PTH	0.001	1,001	0.998-1,003	0.651

HR: Hazard ratio, CI: Confidence interval, PTH: Parathyroid hormone, BMI: Body mass index, CaxP: Calcium phosphate product, BUN: Blood urea nitrogen

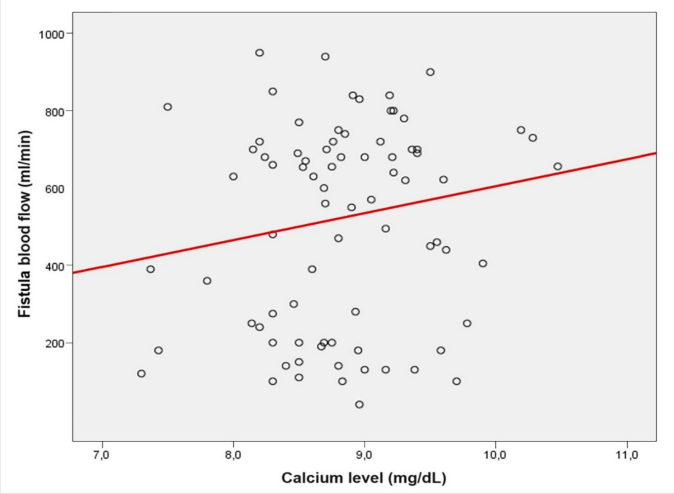

Figure 1. The correlation analysis of calcium levels and fistula blood flows is shown in the scatter plot

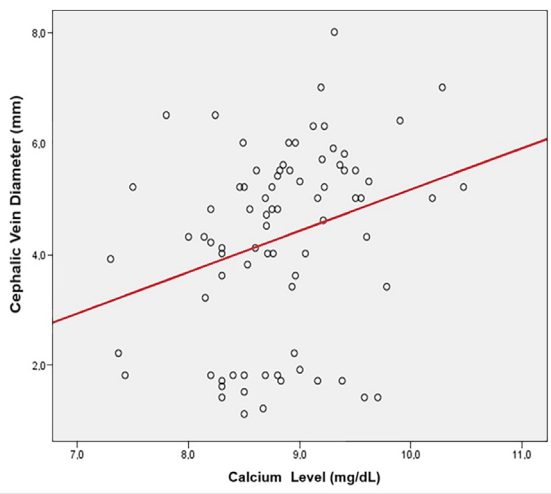

Figure 2. The correlation analysis between calcium levels and access vein diameters is shown in a scatter plot

Table 3. The results of ROC analysis

Parameter	ROC statistics		Diagnostic statistics			
	AUC (95% CI)	p	SEN (95% CI)	SPE (95% CI)	PPV (95% CI)	NPV (95% CI)
Calcium (>8.7 mg/dL)	65.0 (52.4-77.6)	**0.027**	70.0 (46.5-92.5)	59.6 (38.9-76.5)	70.6 (54.6-87.7)	48.3 (31.3-74.8)

AUC: Area under the curve, ROC: Receiver operating characteristic, CI: Confidental interval, SEN: Sensitivity, SPE: Specificity, PPV: Positive predictive value, NPV: Negative predictive value

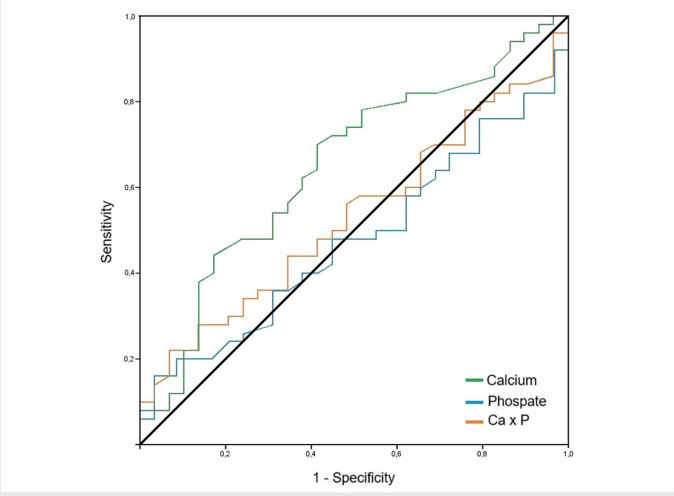

Figure 3. The predictor power of parameters for AVF maturation with ROC curve
AVF: Arteriovenous fistula, ROC: Receiver operating characteristics, CaxP: Calcium phosphate product

Discussion

HD efficacy first depends on sufficient vascular access. Therefore, vascular access was described as the Achilles' heel of HD in clinical practice. AVF is the preferred vascular route in HD practice. Long-term patency and lower complication risk make it stand out. However, maturation failure was an undesired result of the AVF creation.

In this study, we have focused on the possible impact of calcium and phosphate metabolism on AVF maturation in pre-dialysis CKD patients. We analyzed these two clinical situations from different perspectives. Serum calcium concentration, serum phosphate concentration, CaxP value, PTH, hypocalcemia status, and hyperphosphatemia status were among the utilized parameters in analyses. Maturation status, vessel diameters, and fistula blood flow were analyzed in vascular access evaluation.

First, we identified significantly higher serum calcium levels in patients with mature AVF than in patients with immature AVF. Nevertheless, hypocalcemia frequency was higher in patients with immature AVF, but it was not statistically significant. Lastly, we determined a positive correlation between serum calcium levels and cephalic vein diameters. However, no relevance was not identified between serum phosphate or CaxP and AVF maturation.

In this study design, we imposed several limitations in patient selection. Patients with a radiocephalic AVF location should be in the predialysis period. Only one location option was used to minimize anatomic risk factors. Previous studies reported distinct AVF locations with different maturation rates. Additionally, undergoing dialysis has been reported as a factor affecting AVF maturation. In addition, long-term dialysis history has been associated with deterioration of the vascular structure. This elimination was preferred because the variability in dialysis durations among patients could significantly influence the results.

However, a review of the literature revealed that studies investigating AVF maturation predominantly focused on patients undergoing HD treatment (2,6). From this standpoint, we believe the current findings offer significant value.

Both the presence of DM and advanced age were associated with poor outcomes in the AVF maturation process in our cohort. We determined a statistically higher frequency of immature AVF (58.6%) in diabetic participants. In fact, the mentioned results were also, consistent with the literature. DM was reported as a significant negative predictor of venous remodeling in dialysis patients. DM can lead to a pro-thrombotic state, endothelial injury, and extracellular matrix expansion on vasculature (7). The mentioned alterations could contribute to thrombosis and stenosis in AVF. The outcomes of numerous studies show that elderly patients with radiocephalic AVF had increased primary failure rates and decreased patency (8).

In our cohort, the presence or absence of HT was not associated with AVF maturation. Furthermore, the frequency of PVD among our patients was quite low (5 patients). This may be related to the study design, because only patients with radiocephalic AVF were included, excluding primarily non-functioning fistulas. Therefore, we could not analyze the effect of PVD on AVF maturation.

In CKD, the clinical importance of hypocalcemia and hyperphosphatemia extends beyond electrolyte imbalance. These disturbances are associated with poor clinical outcomes and are closely linked with increased mortality in CKD. Despite these electrolyte disturbances being separate entities, they are also components of the main clinical condition defined as CKD-MBD. The cardiovascular system is severely affected by these electrolyte disturbances. Hypocalcemia is an independent predictive factor for cardiac dysfunction in patients with CKD (9). Increased phosphate levels induce HT, vascular calcification, cardiac valvular calcification, atherosclerosis, left ventricular hypertrophy, and myocardial fibrosis in CKD (10). Furthermore, CaxP is a clinically relevant tool in CKD to estimate the vascular risk of patients (11).

A high frequency of hypocalcemia (21.5%) was determined, and only 66.4% of individuals diagnosed with hypocalcemia used calcitriol serum calcium levels should be corrected with medications during the predialysis period, as well as during the dialysis period in CKD patients. It is probably overlooked because most cases are asymptomatic. However, our findings highlight the differential importance of hypocalcemia and the implications of its management. In the advanced stages of CKD, KDIGO guidelines recommend monitoring for serum calcium and phosphate every 1-3 months and targeting normal serum calcium levels (5).

Although AVF is the most preferred type of vascular access, the increased AVF failure rate has been remarkable in recent years (12). Identifying risk factors for AVF failure in advance may provide therapeutic benefits. An accomplished AVF maturation requires functional and structural adaptations in the inflow artery and outflow vein. The physiology of the AVF maturation process is complicated and largely unclear. The blood is shunted into the vein after AVF creation and the increased blood flow leads to vein remodeling. The increased blood flow results in augmented vessel wall shear stress and induces vasodilation in the vein. Nitrous oxide and matrix metalloproteinases are essential in this step (13). The main cause of maturation failure is an anatomic problem, such as vascular stenosis (14).

We analyzed the preoperative status of the two amenable electrolytes in the AVF maturation process. Hypocalcemia could emerge through distinct mechanisms in CKD, such as vitamin D deficiency and hyperphosphatemia. Hypocalcemia typically does not occur until eGFR <15 mL/min. In one study, the frequency of hypocalcemia was reported as 23.6% in patients with advanced CKD (15). The hypocalcemia frequency was found to be 21.5% in our results, and this rate was consistent with existing literature.

In previous studies, we encountered confusing results about the relationship between serum calcium concentration and AVF maturity. Kubiak et al. (16) reported that serum mineral concentrations were not associated with major histological characteristics of veins or AVF maturation failure. However, Moon et al. (17) identified hyperphosphatemia as an indicator of AVF maturation failure and shortened AVF patency in dialysis patients. In another study, high CaxP values were associated with an increased risk of AVF failure by causing arterial stiffness in dialysis patients (18). Furthermore, higher serum PTH levels lead to an increase in the risk of AVF maturation failure through the transition of vascular smooth muscle cells to myofibroblasts (19). On the contrary, Masengu et al. (20) reported that arterial stiffness (measured by invasive methods) was not associated with AVF maturation.

The underlying explanation for the current results remains unclear. However, it can be hypothesized that the smooth muscle cell layer in the vessel wall may be influenced by serum calcium levels during the vessel dilatation phase. Calcium ions are known to be essential for smooth muscle function (21). Moreover, decreased calcium levels are both an indicator and a component of CKD-MBD, which is a recognized risk factor for VC. Also, VC could impede the adequate dilatation of the feeding artery, a process essential for successful AVF maturation. Nevertheless, the outcomes related to serum phosphate levels appear inconsistent with the literature, potentially because our laboratory data were obtained during the pre-dialysis period. Additionally, phosphorus levels in our study were not markedly elevated, with an average serum phosphate concentration of 4.1 mg/dL, which is within the normal range. It is worth noting that the majority of existing studies have been conducted in populations undergoing maintenance HD (6).

Study Limitations

Firstly, several laboratory parameters could be added to the analysis, such as 25-dihydroxyvitamin D level, alkaline phosphatase, and FGF-23 level. Increased patient numbers ensure more accurate results, although it's worth noting that similar studies in the literature have reported comparable patient numbers. Another limitation is the absence of CKD-MBD treatment, such as phosphate binders or calcitriol.

Conclusion

Although numerous risk factors for AVF maturation failure have been identified, we underscored an amenable factor. Maintaining optimal serum calcium levels should be considered a potential contributor to improving AVF patency in patients scheduled for HD.

Ethics

Ethics Committee Approval: This study has been approved by the Erciyes University Health Sciences Research Ethics Committee (approval number: 2024/269, date: 04.12.2024).

Informed Consent: Retrospective study.

Footnotes

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

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

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Anesthesia Management of Pediatric Burn Patients: A Retrospective Analysis of Patients Treated in a University Hospital

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ABSTRACT

Introduction: This retrospective study focused on pediatric patients who underwent surgery for burns under anesthesia in our hospital and assessed demographic data, anesthesia management, and risk factors for mortality. The study comprised 278 pediatric patients who were treated in our unit, a major center for burn admissions, between January 2012 and May 2021. All the patients had burns involving more than 10% of the total body surface area.

Methods: Data on the following were collected: patient age, sex, and ethnicity; anesthesia and airway management- and surgery-related procedures; and laboratory test results. The data on the fatal and non-fatal cases and those with/without head and neck burns were compared.

Results: The mean age of the patients was 56.8±42.9 months (range 1-204 months). The number of patients with flame burns was statistically, significantly higher than the number of patients with liquid and electrical burns (54.7%, 37.1%, and 8.3%, respectively) ($p<0.001$). Albumin ($p=0.046$), platelet ($p=0.005$), and calcium ($p=0.001$) values were significantly lower, and blood urea nitrogen ($p=0.024$) and C-reactive protein ($p=0.001$) values were significantly higher in mortality cases than in non-mortality cases. Patients who died were statistically significantly younger ($p=0.023$). For airway management, endotracheal intubation and sugammadex were used significantly more often for head and neck burns than for other types of burns ($p<0.001$).

Conclusion: Appropriate preoperative preparation, including consideration of the anesthetic method and potential complications that may develop during the surgery, is needed in pediatric burn cases. Anesthesia and airway management are important in managing pediatric burn patients.

Keywords: Burn injury, pediatric, mortality, anesthesia, airway device, head-neck burn

Introduction

The skin provides a protective barrier against infections and fluid loss. Burn-induced damage of this barrier increases the risk of infection and fluid regulation disturbances, with the risk increasing with the degree of the burn. Burns can also lead to physiopathological changes in organs and systems (1). Burns can lead to physiopathological changes in organs and systems, depending on the degree of burn. Burn-related changes affecting the cardiovascular system include tachycardia and hypertension. Conditions affecting the pulmonary system include pulmonary hypertension, pulmonary edema, and a decrease in mucociliary activity, which is due to the release of pulmonary system mediators. These changes cause an increase in the incidence of clinical laryngospasms, bronchospasms, and pneumonia (2). In cases of hepatic damage due to burns, elevated liver enzymes and coagulation disorders, such as disseminated intravascular coagulopathy and thrombocytopenia, may develop. Thus, burns are an important cause of mortality and morbidity (3).

Knowledge of burn-related pathophysiological changes is important for the anesthetic management of burn patients. For example, impairment of hepatic and renal clearance due to burns has implications for the pharmacodynamic and pharmacokinetic effects of many pharmacological agents, especially muscle relaxants, which complicates anesthesia management (4). Airway management in children is more difficult than in adults due to their shorter chin, neck, and trachea, in

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addition to the narrowness of the cricoid cartilage and the increased length of the epiglottis. In addition, pathologies, such as burn-induced contractures in the head-neck and chest wall and subglottic stenosis, especially during the recovery period, make mask ventilation and intubation difficult in the pediatric population (5).

Bleeding and fluid loss are the most common complications of burn surgery. Early surgical debridement can reduce blood loss. Fluid replacement is critical for organ perfusion. During anesthesia management, urine output, blood pressure, central venous pressure, and the acid-base balance must be maintained. Blood and fluid replacement are also vital (5).

The purpose of this study was to retrospectively investigate anesthesia management and factors affecting mortality in a pediatric population who underwent burn surgery under anesthesia in our unit between January 2012 and May 2021.

Methods

Study Population

This study included pediatric patients (n=305) who underwent surgery under anesthesia for burns at İnönü University Medical Faculty Hospital (Malatya, Türkiye) between January 2012 and May 2021. Twenty-seven patients with missing hospital records and anesthesia follow-up were not included in the study, as shown in the flow diagram (Figure 1). The final study included 278 pediatric patients with burns involving ≥10% of the total body surface area (TBSA).

Study Protocol

The Non-interventional Clinical Research Ethics Committee of İnönü University approved this study, and the study was prepared in accordance with the Consolidated Standards for Reporting Studies (CONSORT) (6) (approval number: 2022/2818, date: 11.01.2022).

Preoperative Procedures

As premedication, midazolam (dose: 0.5 mg/kg) was administered periorally, as all the patients were older than 1 year and therefore not expected to have a difficult airway. As standard, in all surgical cases, mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2), and end-tidal carbon dioxide pressure ($EtCO_2$) monitoring was performed. Electrocardiogram monitoring was performed in all cases, except for patients with severe trunk burns.

Anesthesia Management

An experienced anesthesiologist was in charge of the anesthesia protocol. Propofol (0.5-2 mg/kg), pentothal (5 mg/kg), ketamine (1-2 mg/kg), or ketofol was administered intravenously (IV) for induction of anesthesia after preoxygenation (100% 5 L/minute oxygen for 3 minutes; 1 mg/kg ketamine and propofol mixture, IV). Rocuronium (0.4-0.6 mg/kg) or vecuronium (0.1 mg/kg) was used as a muscle relaxant. Fentanyl (0.5-1 µg/kg) was administered for analgesia during anesthesia induction.

Anesthetic drugs were administered in appropriate doses according to ideal body weight. Ventilation parameters were set to ensure a tidal volume of 6-8 mL/kg and $EtCO_2$ value of 35-45 mmHg. Anesthesia maintenance was provided by inhalation of desflurane or sevoflurane in a 50% oxygen-nitrous oxide mixture. Atropine (0.01-0.20 mg/kg, IV) and neostigmine (0.05 mg/kg, IV) or sugammadex (2-4 mg/kg, IV) were administered to reverse residual muscle relaxation at the end of the surgery.

Patients who opened their eyes in response to a stimulus at the end of the surgery had regular spontaneous breathing, and had SpO_2 of >95% were extubated and taken to the postanesthesia care unit. Patients who were hemodynamically unstable or did not show sufficient respiratory effort after the surgery were intubated and taken to the intensive care unit (ICU).

Outcome Measures

Demographic data on the patients, duration of the anesthesia and surgery, length of stay in the hospital and ICU, cause of burn, burn site, mortality, biochemical data [i.e., glucose, C-reactive protein (CRP), blood urea nitrogen (BUN), albumin, hemoglobin, and platelets], and anesthesia management data were recorded. Anesthesia follow-up data were obtained from the hospital's database. Values for HR, MAP, and SpO_2, along with time intervals T0 (preanesthesia), T1 (5 minutes after intubation), T2 (perioperative 30th minute), and T3 (end of procedure), were recorded. $EtCO_2$ was measured at T1 and T2 time intervals.

Procedural Data

The anesthesia duration was defined as the time from induction to conscious response to verbal commands after the surgical procedure. The time of the surgical procedure was determined as the time from removing the dressing to incision closure. Length of stay was considered as the time elapsed from the patient's admission to the hospital until discharge or death. The ICU duration was determined as the time from admission after anesthesia to the ICU to discharge or death. Hospital mortality was defined as in-hospital death postsurgery.

Postoperative Management

Postoperatively, the patients were observed in the postanesthesia care unit. When a modified Aldrete score of ≥9 was achieved, the patient was transferred to the relevant service (7). For postoperative analgesia, morphine (0.05-0.1 mg/kg, IV), tramadol (0.5-1 mg/kg, IV), or paracetamol (15 mg/kg, IV) was administered in all cases.

Statistical Analysis

Data are displayed as mean, standard deviation, or frequency (percentage). The normality distribution of the data was determined using the Shapiro-Wilk test. Qualitative data, were evaluated by Yates-corrected chi-square test, Pearson's chi-square test, or Fisher's exact test, when appropriate. Pairwise comparisons were analyzed using Pearson's chi-square test with Bonferroni correction. Normally distributed data were compared using an Independent samples t-test. Data where $p<0.05$ were considered statistically significant. IBM SPSS statistics version 25.0 for Windows (New York, USA) was used for statistical analysis. The superscripts a and b indicate the statistical significance of the column proportions at the 0.05 level in the figures.

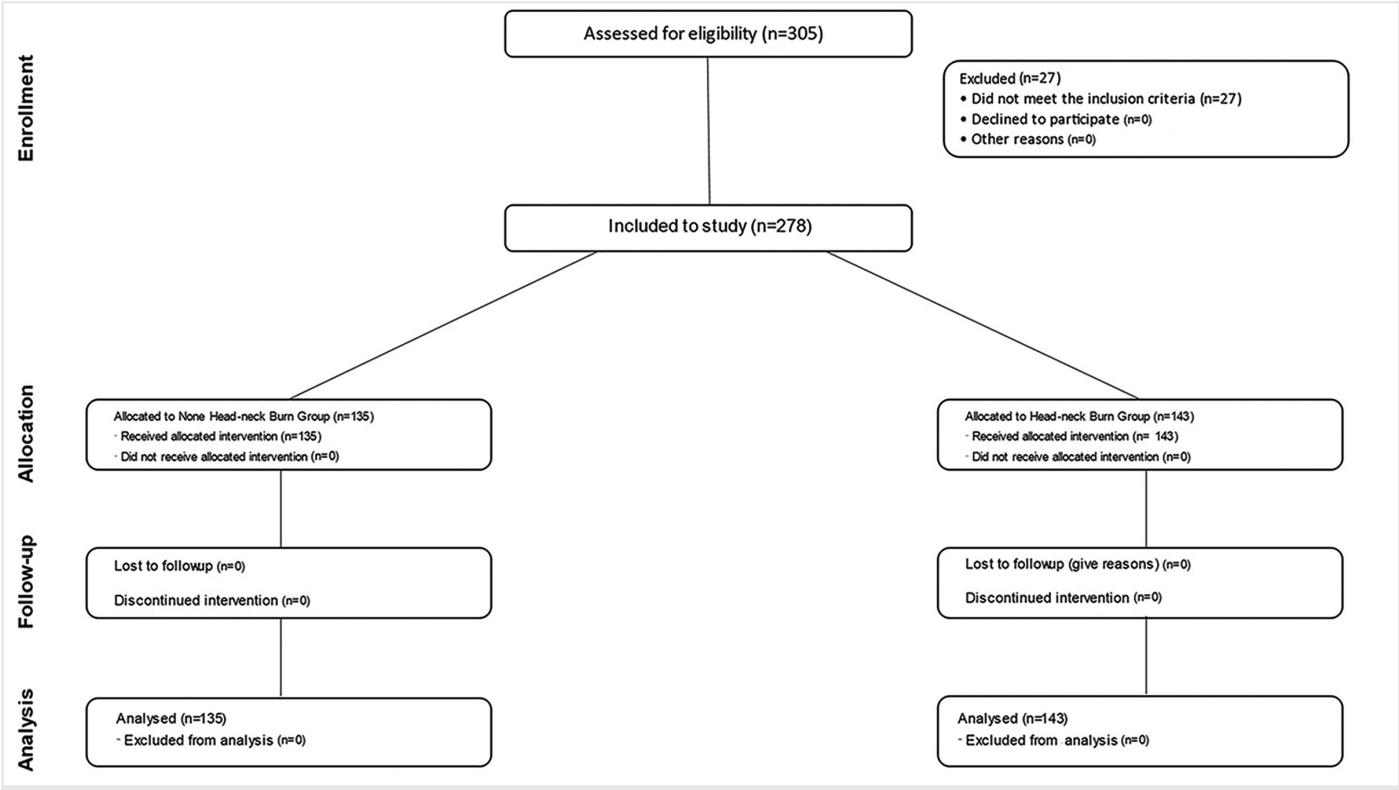

Figure 1. Consort diagram

Results

The mean age of the patients was 56.8±42.9 months (range 1-200). Of the 278 patients, 159 (57.1%) were males, and 119 (42.9%) were females. In total, 133 (47.8%) patients were Turkish citizens, and 145 (52.2%) patients were Syrian nationals.

The number of flame burns was significantly higher than the number of liquid and electrical burns (54.7%, 37.1%, and 8.3%, respectively) ($p<0.001$) (Table 1). The time to hospital discharge (35.2±5.8 days) and ICU stay (35.1±5.8 days) was longer in the flame burn group, with a statistically significant difference ($p<0.001$).

In terms of surgical interventions, the findings were as follows: graft (n=206, 74.1%), debridement (n=60, 21.6%), graft plus amputation (n=5, 1.8%), contracture opening (n=4, 1.4%), flap (n=2, 0.7%), and dressing (n=1, 0.4%). Eleven patients died during the study period (January 2012-May 2021) (mortality rate: 4%). Demographics and procedural-related data are shown in Table 1.

In total, 1.1% of the patients were taken to the operating room while intubated. In 91.5% of cases, general anesthesia was administered. Regional anesthesia or sedoanalgesia was administered in 7.8% and 0.7% of cases, respectively. Oral endotracheal intubation was used in 66.3% of cases, and laryngeal mask airway (LMA) was used in 33.1% of cases. Table 2 provides information on anesthesia management and the mean biochemical values in the laboratory tests.

When we compared the preoperative laboratory values of the mortality and non-mortality cases, the mortality cases were characterized by statistically significantly lower albumin ($p=0.046$), platelet ($p=0.005$), and calcium ($p=0.001$) values and higher BUN ($p=0.024$) and CRP ($p=0.001$) values. The length of hospital stay and ICU stay were shorter among the mortality cases than the non-mortality cases ($p<0.001$). Younger age was significantly associated with mortality ($p=0.023$). Table 3 provides details on the characteristics of the mortality and non-mortality cases.

In terms of the intubation tools used in airway management of the patients with head and neck burns, there was a significant difference in the use of video laryngoscope (VL), LMA, fiberoptic bronchoscope, and direct laryngoscope ($p<0.05$). The results associated with the use of airway devices were not statistically significant (Table 4). The use of endotracheal intubation in the patients with head and neck burns was significantly higher than in those without ($p<0.001$).

The use of rocuronium, a muscle relaxant agent employed in anesthesia induction, was significantly higher in the patients with head and neck burns than in those without head and neck burns ($p<0.001$). The use of sugammadex to reverse the effects of the muscle relaxant was significantly higher in patients with burns of the head and neck than in patients without head and neck burns ($p<0.001$). Head and neck burns were significantly more common among patients of Syrian origin than among those of Turkish origin ($p<0.001$). When the cause of burns was examined, the most common cause was flame burns ($p<0.001$). Characteristics of the face and neck burns are given in Table 5. Figure 2 shows the hemodynamic data of the patients measured at specified times.

Discussion

In this study we evaluated pediatric patients who underwent surgery for burns in our unit, and more than half the patients were foreign nationals. Flame burns were the most frequent, and the most common surgical procedure was the opening of contractures. General anesthesia was applied in the majority of cases. Propofol was preferred as the IV anesthetic agent, and sevoflurane was preferred as the inhalation agent. The use of sugammadex to reverse the effects of muscle relaxants was significantly higher in patients with burns of the head and neck than in patients without these types of burns. The overall mortality rate during the study period was 4%.

Burns are generally more common among boys than girls. In a previous retrospective study, males accounted for 62% of burn cases (8). In another study, 52% of burn cases were male (9). In our study, 57.1% of the burn patients were males, which is consistent with the literature. There is a predominance of face and neck burns, with 58% occurring in males and 42% in females. The preponderance of Syrian burn patients

Table 1. Demographics and procedure data

Gender, n (%)	
Male	159 (57.1)
Female	119 (42.9)
Age (month)	56.8±42.9
ASA score, n (%)	
I	41 (14.7)
II	200 (71.9)
III	36 (12.9)
IV	1 (0.4)
Nationality	
Turkish	133 (47.8)
Syrian	145 (52.2)
Burn cause, n (%)	
Flame	152 (54.7)
Liquid	103 (37.1)
Electric	23 (8.3)
Type of surgery, n (%)	
Debridement	60 (21.6)
Graft	206 (74.1)
Dressing	1 (0.4)
Graft + amputation	5 (1.8)
Contracture	4 (1.4)
Flap	2 (0.7)
Burn percentage, %	40.1±15.9
Duration of surgery, min.	58.7±24.8
Duration of anesthesia, min.	69.7±27.1
Length of hospital stay, day	83.5±48.5
Length of ICU, day	78.7±48.8
Mortality, n (%)	11 (4)

n: Number, %: Percantage, ASA: American Society of Anesthesiologists, ICU: Intensive care unit, Min.: Minimum

Table 2. Anesthesia management characteristics and laboratory data

Coming with entubation, n (%)	3 (1.1)
Premedication, n (%)	37 (13.3)
Position, n (%)	
Supine	264 (95)
Prone	12 (4.3)
Lateral	1 (0.4)
Supine + prone	1 (0.4)
Anesthesia management, n (%)	
Sedoanalgesia	2 (0.7)
Regional anesthesia	22 (7.8)
General anesthesia	254 (91.5)
Entubation management, n (%)	
None	2 (0.7)
Oral	184 (66.3)
LMA	92 (33.1)
Exit as intubated, n (%)	2 (0.7)
IV anesthetic used in induction, n (%)	
None	1 (0.4)
Propofol	182 (65.5)
Thiopental	13 (4.7)
Propofol + ketamin	81 (29.1)
Propofol + thiopental	1 (0.4)
Opioid used in induction, n (%)	
Fentanyl	260 (93.5)
Remifentanyl	18 (6.5)
Neuromuscular drug used in induction, n (%)	
None	98 (35.3)
Rocuronium	172 (61.9)
Vecuronium	8 (2.9)
Neuromuscular reversing drug used in induction, n (%)	
None	98 (35.3)
Neostigmine	170 (61.2)
Sugamadex	10 (3.6)
Postoperative analgesic drug, n (%)	
Contramal	23 (8.3)
Morphine	78 (28.1)
Paracetamol	38 (13.7)
Contramal + paracetamol	28 (10.1)
Morphine + paracetamol	111 (40)
Central catheterization, n (%)	15 (5.4)
Blood transfusion, n (%)	70 (25)
CRP (mg/L)	5.2±6.1 (0.2-32)
Glucose (mg/dL)	105.8±25.9 (57-321)
BUN (mg/dL)	9.2±4 (2-29)
Creatinin (mg/dL)	0.4±0.6 (0.23-10.68)
Albumine (g/dL)	2.6±0.7 (0.8-4.6)
Platelet (10^3 cell/mL)	470.1±175.1 (22-1128)
Hemoglobine (g/dL)	10.6±1.7 (6.6-15.9)

n: Patient number, LMA: Laryngeal mask, IV: Intravenous, CRP: C-reactive protein, BUN: Blood urea nitrogen

(52.2%) in our study is likely due to the high number of immigrants in Türkiye and our unit being a major center for burn admissions.

Among burn patients requiring surgery, airway management is one of the main issues complicating anesthesia management, with a high risk of airway edema and respiratory failure, especially in patients with head and neck burns. In these patients, a low-pressure, cuffed endotracheal tube should be used when intubation is indicated to reduce air leakage together with positive pressure ventilator strategies (10). Although the use of a cuffed endotracheal tube in pediatric patients is associated with a risk of tracheal mucosal ischemia and postextubation stridor, this risk can be minimized by using an appropriately sized tube and low cuff pressure (11). In our study, a cuffed endotracheal tube was employed in 68.5% of cases, with an uncuffed endotracheal tube used in the other cases (31.5%). The majority of head and neck burns are caused by flame exposure, which results in inhalation injury.

An airway evaluation should be undertaken before intubation, especially in pediatric patients with head and neck burns because of burn-related edema and exudate on the face. During anesthesia induction, various factors, including facial lesions, nasogastric tubes, and topical antibiotics, complicate mask ventilation. Edema in the glottic and subglottic region due to inhalation burns, and contractures that prevent mandibular and neck mobility makes endotracheal intubation and airway management difficult (12,13). In addition, upper airway obstruction due to edema may cause the airway to collapse during anesthesia induction and make ventilation impossible. For these reasons, alternatives to VL, LMA, and fiberoptic intubation methods should be considered, including awake intubation, for patients with head and neck burns. Surgical release of neck contractures and the possibility of a tracheostomy should also be considered in this population. Waymack et al. (14) reported that a tracheostomy was performed in four neck contracture cases, despite the surgical opening being performed for the contracture. In our study, irrespective of burn type, none of the patients required a tracheostomy for airway management. We attribute this to the use of VL, LMA, and fiberoptic intubation methods in our clinic.

Table 3. Comparison data of cases with and without mortality

	Absent n=267	Present n=11	p-value
Age (month)	55.7±41.9	87.2±58.0	**0.023**
Length of hospital stay, day	84.9±48.9	48.1±16.0	**0.014**
Length of ICU, day	81.17±48.2	20.36±12.0	**<0.001**
Burn percentage, %	39.21±14.6	63.18±26.6	**<0.001**
Glucose (mg/dL)	105.3±25.8	118.6±24.2	0.096
BUN (mg/dL)	9.1±3.8	11.9± 6.4	**0.024**
Creatinin (mg/dL)	0.4± 0.6	0.4±0.1	0.839
Albumine (g/dL)	2.68±0.78	2,2±0.79	**0.046**
Platelet (10^3 cell/mL)	476±173.3	325.4±163	**0.005**
Hemoglobine (g/dL)	10.6±1.7	10.5±2.5	0.970
CRP (mg/L)	4.7±5.6	16.8±6.6	**<0.001**
Calsium	9.3±0.8	8.1±0.8	**0.001**

ICU: Intensive care unit, n: Number, %: Percentage, BUN: Blood urea nitrogen, CRP: C-reactive protein

Table 4. Characteristics of devices used in airway management

Head-neck burn			
Airway devices	**None n (%)**	**Present n (%)**	**p-value**
DL	43[a] (31.9)	28[a] (19.6)	**<0.001**
VL	18[a] (13.3)	56[b] (39.2)	
LMA	62[a] (45.9)	31[b] (21.7)	
FB	12[a] (8.9)	28[b] (19.6)	
Total	135 (100.0)	143 (100.0)	

[a,b]: Different superscript letters denote significantly different column proportions at the 0.05 level. DL: Direct laryngoscopy, VL: Video laryngoscope, LMA: Laryngeal mask airway, FB: Fiberoptic bronchoscope

Previous studies reported many potential benefits of regional anesthesia in burn cases, especially in the postoperative period, due to its analgesic effects (15,16). In our study, general anesthesia was applied in 91% of cases and regional anesthesia was applied in 7.8% of cases. The burn distribution, with the burns located in many areas rather than in a single one, as well as the patient population (i.e., pediatric) may explain the reduced use of regional versus general anesthesia in our study.

Major burns are a significant cause of mortality in the pediatric population (3). Kraft et al. (17) reported mortality in 120 (13%) of 952 pediatric burn patients. In their study, the mortality rate was 7 (3%) of 260 cases with 40-49% TBSA burns, 12 (7%) of 171 cases with 50-59% TBSA burns, and 19 (22%) of 85 cases with 70-79% TBSA burns. They reported that the incidence of mortality increased as the TBSA burn increased. In our study, the TBSA burn was 40.1±15.9%, and 11 (4%) of the 278 patients died.

The mortality rate for patients with head and neck burns was 5.6% in our study. When we compared the preoperative laboratory values of the mortality and non-mortality cases, the mortality cases were characterized by statistically significantly lower albumin ($p<0.046$), platelet ($p<0.005$), and CRP ($p<0.001$) values, and statistically significantly higher BUN values ($p<0.024$). These results point to a significant relationship between laboratory values and mortality in burn cases. In addition, we found a significant relationship between mortality and burn percentage, time to hospital discharge, length of stay in the ICU, burn site (head and neck), and age. In another study, burn percentage, burn type, and age were risk factors for mortality among pediatric burn cases (18).

During the acute phase of a burn, systemic edema affects hemoconcentration, causing an increase in hematocrit, and blood viscosity. Anemia may occur later due to hemolysis of erythrocytes caused by the burn-induced rise in the temperature, blood loss in the wound area, and dilution due to fluid resuscitation (3). Burns, also lead to changes in hemoglobin, and excision and grafting interventions in burn surgery cause high blood loss, depending on the size of the surgical area (19). Thus, a blood transfusion is frequently necessary in pediatric burn cases (20). Wittenmeier et al. (21) reported that 11 (22.4%) of 138 pediatric burn cases, with a mean age of 21 (9-101) months and TBSA burn of 30%, required a blood transfusion. In a mixed multicenter retrospective study consisting of adult and pediatric burn cases, 75% of patients with TBSA burns of >20% received a blood transfusion (22).

Table 5. Characteristics of head-neck burn

Characteristics	Head-neck burn		p-value
	None (n=135)	Present (n=143)	
ASA score, (I/II/III/IV)	19/99/16/1	22/101/20/0	0.793
Arterial monitoring, n (%)	135 (48.6)	143 (51.4)	0.788
Gender, (M/F), n (%)	76/58 (56.7/43.3)	83/60 (58/42)	0.903
Coming with entubation, n (%)	2 (1.5)	1 (0.7)	0.613
Entubation management, n (%), (none/oral/LMA)	1/73/61 (0.7/54.1/45.2)	1/111/31 (0.7/77.6/21.7)	**<0.001**
IV anesthetic used in induction, n (%) (propofol/thiopental/propofol + ketamin/propofol + thiopental)	1/96/6/32/0 (0.7/71.1/23.7/0)	0/86/7/49/1 (0/60.1/34.3/0.7)	0.141
Neuromuscular drug used in induction, n (%), (none/rocuronium/vecuronium)	64/68/3 (47.4/50.4/2.2)	34/104/5 (23.8/72.7/3.5)	**<0.001**
Opioid used in induction, n (%) (none/fentanyl/remifentanyl)	5/128/2 (3.7/94.8/1.5)	11/132/0 (7.7/92.3/0)	0.099
Mortality, n (%)	3 (2.2)	8 (5.6)	0.219
Position, n (%) (supine/prone/lateral/supine + prone)	123/11/0/1 (91.1/8.1/0/0.7)	141/1/1/0 (98.6/0.7/0.7/0)	**0.002**
Neuromuscular reversing drug used in induction, n (%) (none/neostigmine/sugammdex)	64/69/2 (47.4/51.1/1.5)	34/101/8 (23.8/70.6/5.6)	**<0.001**
Central catheterization, n (%)	5 (3.7)	10 (7)	0.291
Nationality, n (%), (Turkish/Syrian)	86/49 (63.7/36.3)	47/96 (32.9/67.1)	**<0.001**
Burn cause, n (%), (flame/liquid/electric)	48/71/16 (35.6/52.6/11.9)	104/32/7 (72.7/22.4/4.9)	**<0.001**
Presence of difficult airway, n (%)	133/2 (98.5/1.5)	136/7 (95.1/4.9)	0.714
Uncuffed/cuffed ETT, n (%)	32 (43.9)/41 (56.1)	13 (11.8)/98 (88.2)	**<0.001**

ASA: American Society of Anesthesologists, n: Number of patient, M: Male, F: Female, LMA: Laryngeal mask airway, IV: Intravenous, ETT: Endotracheal tube

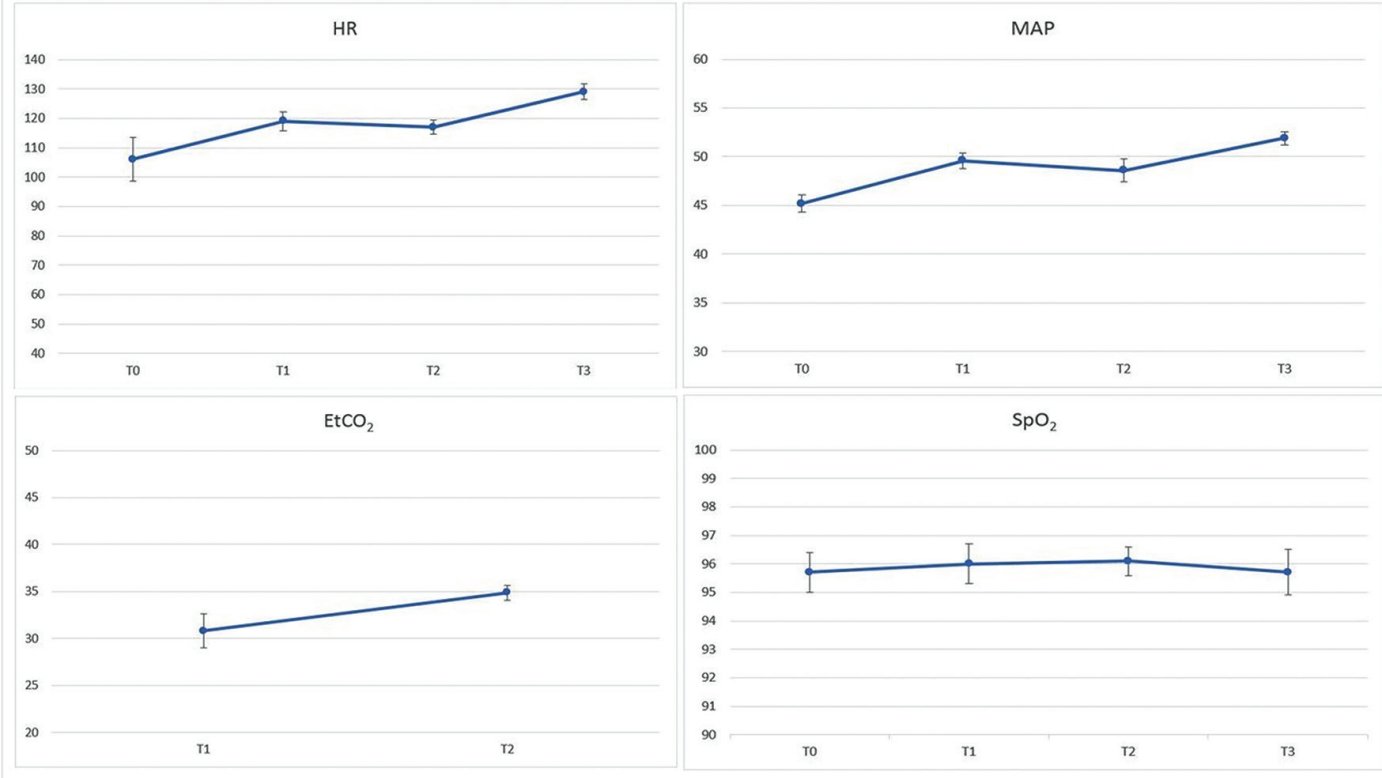

Figure 2. Hemodynamic data of patients (HR, MAP, $EtCO_2$ ve SpO_2)
T0: Before anesthesia, SpO_2: Peripheral oxygen saturation, $EtCO_2$: End-tidal carbon dioxide pressure, MAP: Mean arterial pressure, HR: Heart rate

In our study, 70 (25%) of the 278 patients required a blood transfusion. Differences in the average age of the patients and percentage of TBSA burn may explain the variability in reported blood transfusion rates.

Muscle relaxants are used in burn cases. The muscle relaxant dosage may need to be adjusted due to potential drug resistance. Burn patients may show an excessive hyperkalemic response as a result of hypersensitivity to succinylcholine (23). Therefore, potassium values should be taken into account in the preanesthetic evaluation. In our study, succinylcholine was not used because of the possibility of a hyperkalemic response.

At least 50% of burns in the general population (i.e., children and adults) are located in the head and neck region. Male sex, young age, and flame burns are the primary risk factors for head and neck burns in the general population (24). In our study, the patients were divided into two groups according to the presence or absence of head and neck burns. In line with the literature, 51.4% of our patients had head and neck burns. In our pediatric population, 58% of the patients with head and neck burns were males, and a flame was the cause in 72.7% of cases.

Neostigmine is widely used to reverse neuromuscular blockade in general anesthesia. In a previous study that compared adverse effects of sugammadex and neostigmine, sugammadex was associated with fewer cardiovascular, respiratory, and postoperative side effects (25). In a review of 26 studies on the reversal of neuromuscular blockade using sugammadex or neostigmine, sugammadex reversed neuromuscular blockade faster and was safer than neostigmine (26). In our study, sugammadex was used significantly more frequently in patients with head and neck burns than in patients with other types of burns ($p<0.001$). We attribute the use of sugammadex in these patients to concerns about the risk of cardiac, respiratory, and postoperative side effects. In the present study, the use of rocuronium was significantly higher among patients with head and neck burns than among patients without these types of burns ($p<0.001$). According to previous research, sugammadex rapidly reverses the neuromuscular blockade effects of rocuronium, suggesting that sugammadex may be useful for airway management and reducing postoperative complications (e.g., edema, ventilation and intubation difficulties, limited mouth opening, and restrictions in neck movements due to contracture) (25,26). Endotracheal intubation may be preferable to sugammadex for pediatric burn patients due to safer airway management and other factors (e.g., aspiration, edema, or air leakage) associated with sugammadex that complicate ventilation (27). In this study, the use of oral endotracheal intubation was statistically, significantly higher among patients with head and neck burns than among patients without these types of burns.

Study Limitations

This study has a few limitations. First, the small number of patients is a limitation. Second, the study included only pediatric patients. A further study should investigate whether similar results would be found in an adult population. In addition, this was a single-center study. A multicenter study would have shed light on the outcome of anesthetic management and surgical methods in a range of settings. Finally, this was a retrospective study. A prospective study would have required more specific information regarding the exact variables or data needed for analysis.

Conclusion

There is a significant relationship between mortality and the burn percentage, length of hospital stay, length of stay in the ICU, burn site (face and neck), and younger age. We conclude that the use of VL, LMA, and fiberoptic intubation methods, especially in airway management of head and neck burns, may reduce the need for a tracheostomy in pediatric burn patients. Appropriate preoperative preparation is needed in pediatric burn cases, with such preparation including consideration of anesthetic management methods and potential surgery-related complications.

Ethics

Ethics Committee Approval: The Non-interventional Clinical Research Ethics Committee of İnönü University approved this study (approval number: 2022/2818, date: 11.01.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - M.D.; Concept - E.K., A.S.Ö.; Design - E.K., M.R.Y., A.S.Ö.; Data Collection or Processing - M.R.Y.; Analysis or Interpretation - E.K., A.S.Ö., Z.B.; Literature Search - E.K., M.R.Y., A.S.Ö., Z.B.; Writing - E.K., A.S.Ö.

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

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Evaluation of Emergency Physicians' Knowledge, Attitudes, and Educational Needs Regarding End-of-Life Patient Management: A Cross-Sectional Survey Study

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ABSTRACT

Introduction: This study evaluates the self-assessed knowledge, attitudes, and educational needs of emergency physicians in Türkiye regarding End-of-Life care (EOLC) to identify barriers and guide training programs.

Methods: A descriptive, cross-sectional survey was conducted between October 7 and December 7, 2024, using a 24-item Turkish questionnaire. The survey included sections on demographics, knowledge, attitudes, and educational needs related to EOLC. Responses were collected via a 5-point Likert scale and multiple-choice questions. The survey was distributed online and in print to 415 emergency physicians, achieving a 48% response rate (n=200).

Results: The majority of respondents (85.5%) reported not having received formal EOLC training, and 41% of them self-assessed their knowledge as inadequate. This self-assessed knowledge was found to be associated with one's professional title. Residents exhibited a higher propensity to report inadequate knowledge compared to specialists (68.5% vs. 25.9%) and faculty members (5.6%) (p=0.021). The importance of privacy for EOLC patients was highlighted by 90% of the participants; 75% expressed support for the involvement of families in decision-making processes; and 70% advocated for the designated "discussion and farewell" room. Key barriers identified included admission barriers, which constituted 20.3% of identified barriers, with 58% rating specialist team support as inaccessible or only partially accessible.

Conclusion: This study identifies areas for improvement in emergency physicians' self-assessed knowledge and training related to EOLC, particularly among those who are younger and less experienced. Formal training was linked to increased confidence and perceived competence. Challenges such as insufficient access to specialist teams and systemic obstacles were noted. The findings point to the potential benefits of advancing EOLC education in emergency medicine curricula through a multidisciplinary approach, which could aid physicians in addressing current limitations and enhancing care delivery.

Keywords: Emergency department, end-of-Life care, end-of-Life, education, survey, palliative care

Introduction

End-of-Life care (EOLC), often associated with palliative care, provides a range of healthcare services designed for individuals in the terminal stages of life. While the term is broadly defined, it may also specifically refer to the care given in the final moments before death (1). Progress in medical advancements and improved chronic disease management has further emphasized the critical role of EOLC. The World Health Organization reports that nearly 40 million people worldwide require palliative care annually; however, only 14% have access to these services (2). This stark disparity highlights the urgent need for healthcare systems to develop and implement policies that ensure fair and accessible palliative care for all (3).

Emergency departments (EDs) frequently act as the first point of care for patients experiencing poorly managed symptoms related to chronic illnesses (4-6). While emergency medicine aims to stabilize patients and manage acute health issues, the focus of EOLC is on improving comfort and ensuring a higher quality of life. The distinct objectives of these two disciplines create significant challenges in incorporating EOLC within the ED setting (7). Obstacles include inadequate staff training, insufficient privacy, heavy workloads, communication difficulties, resource

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limitations, restricted access to specialized palliative care teams, and a low hospital bed turnover rate (8-10).

In Türkiye, the aging population has led to an increase in End-of-Life (EOL) patient admissions, many of whom seek care in EDs (11). Although programs such as the cancer control program and the Pallia-Turk initiative have been introduced, the lack of a unified national policy for palliative care continues to be a significant shortcoming. While hospitals have established EOLC centers and the palliative care nursing certificate program was launched in 2015, the healthcare workforce remains inadequate to address the rising demand (12). Emergency medicine training includes lectures on oncologic emergencies and palliative care, but disparities in patient populations and resource availability across institutions result in inconsistent practical training opportunities.

The purpose of this study is to assess the knowledge, training, and attitudes of emergency physicians toward EOLC. Additionally, it aims to identify gaps in education and offer guidance for designing future training programs.

Methods

Study Design

The study was designed as a descriptive, observational, cross-sectional survey. The questionnaire was developed in Turkish. The study was conducted between October 7th and December 7th, 2024, using online and printed survey methods.

A pilot study was carried out to assess how well the questions were understood. Two professionals not part of the study's target participants completed the questionnaire and offered feedback. Based on their input, minor adjustments were made to the phrasing of the questions.

Participants and Inclusion Criteria

The study population was composed of emergency physicians employed in the Department of Emergency Medicine in university, state, private, and training and research hospitals in İstanbul, İzmir, Ankara, and Bursa, high patient-volume regions of Türkiye.

The number of emergency physicians working per facility varies. Actively working emergency medicine residents, specialists, and faculty members (assistant professors, associate professors, and professors) who provided electronic or written informed consent and completed the survey in full were recruited for the study. Physicians temporarily rotating in EDs from other clinical specialties or those not meeting the inclusion criteria were excluded from the study.

Data Collection Method

Data collection was completed in a 2-month period. The research team contacted the administrative and academic leads of selected emergency medicine clinics by telephone to provide information about the study's purpose and scope. Survey links were distributed to emergency medicine physicians in these clinics via email and internal communication platforms. To enhance participation, a reminder email was sent once, and additional reminders were shared through online platforms. Furthermore, printed survey forms were prepared and distributed in specific centers.

To boost participation, we sent two reminders through mobile communication applications and distributed printed surveys at selected centers. Combining online and printed surveys with multiple reminders effectively increased response rates (13).

Survey Structure

The survey, developed by the researchers following a comprehensive review of the existing literature, was organized into four main sections and comprised a total of 24 questions (14-16). The first section gathered demographic information, including participants' age, gender, professional title, years of experience, workplace type, and prior training in EOLC.

The subsequent sections evaluated participants' knowledge, attitudes, practices, and educational needs related to EOLC. The survey employed two primary question formats: multiple-choice questions and 5-point Likert scale questions. A total of 10 Likert-scale questions were designed to assess participants' agreement with specific statements (e.g., "strongly agree" to "strongly disagree"), their self-evaluated competence in prognosis communication, and their knowledge related to EOLC. The questions also aimed to measure the frequency of encounters with patients requiring EOLC in EDs, the regularity of evaluating organ and tissue donation during EOLC, and the perceived accessibility of specialized support for EOLC decision-making. In addition to these, seven multiple-choice questions were included to allow participants to select one or more relevant responses, focusing on factors influencing EOLC decisions, preferred strategies for pain management, and challenges encountered in the provision of EOLC (refer to Appendix 1).

Participation and Response Rate

The survey invitation link was distributed to 415 emergency medicine physicians via email. A contact person was designated for each facility. The survey link was sent to an initial contact person and then to participants via mobile communication applications. Printed surveys were used to recruit participants during outreach trips to emergency medicine meetings. The participants were encouraged by reminder emails and messages via WhatsApp messenger through the contact person. The responses were obtained from 200 participants. The overall response rate was calculated as 48%. The study was approved by the Non- Interventional Clinical Research Ethics Committee of İstanbul Medipol University (approval number: 919, date: 26.04.2024). Actively working emergency medicine residents, specialists, and faculty members (assistant professors, associate professors, and professors) who provided electronic or written informed consent and completed the survey in full were recruited for the study.

Statistical Analysis

Survey data were organized in Excel and analyzed using SPSS (Version 25.0, IBM Corp., Armonk, NY). Descriptive statistics summarized the data as frequencies, percentages, means ± standard deviation, or medians (minimum-maximum), depending on normality assessed via the Shapiro-Wilk test. The Kruskal-Wallis test, with Dunn-Bonferroni post-hoc analysis, was used for non-normally distributed variables across multiple groups. Categorical data were analyzed using Chi-square and Fisher-Freeman-Halton tests, with a significance threshold of $p<0.05$.

Results

A total of 200 physicians participated in the study, of whom 53.5% were male and 46.5% were female. The mean age of the participants was 33.06±5.68 years. Regarding professional titles, 54% were residents, 37% were specialists, and 9% were faculty members. EOLC training was reported as inadequate, with 85.5% of participants indicating that they had never received formal training, while only 14.5% reported prior training, primarily during their residency programs. Additionally, 75.5% of participants stated that they frequently or very frequently encountered patients requiring EOLC in the ED.

Self-assessment of knowledge in End-of-Life care: Among participants, 41% rated their knowledge as inadequate ("completely inadequate" or "inadequate"), whereas only 13.5% considered their knowledge to be adequate. A statistically significant difference in median age was observed across self-assessed knowledge levels, with participants who rated their knowledge as adequate having a higher median age (p=0.027). Professional title also influenced knowledge competency, with inadequate knowledge reported more frequently by residents (68.5%) compared to specialists (25.9%) and faculty members (5.6%), (p=0.021). Additionally, participants with more than 10 years of experience were significantly more likely to rate their knowledge as adequate (44.4%) compared to those with fewer years of experience (p=0.024). Adequate knowledge was reported by 55.6% of physicians who had received formal EOLC training, compared to 44.4% of those without training (p<0.001). Notably, none of the participants rated their knowledge as "strongly adequate" (Table 1).

End-of-Life care factors in the emergency department: Participants were asked, "what factors do you consider important when evaluating EOLC for ED patients?" Multiple responses were allowed. The most frequently selected factor in evaluating EOLC in the ED was effective symptom control (24.0%), followed by decision-making capacity (18.8%). The importance of the presence of a care team and review of the care plan was equally recognized (17.1% each), while non-pharmacological symptom management was identified as a relevant factor by 15.1% of participants. The availability of palliative care centers was the least frequently selected factor (7.8%) (Figure 1).

Pain assessment methods for End-of-Life care patients: Participants were asked, "which standardized pain scoring system do you use to assess pain in EOLC patients?" The most commonly used standardized pain assessment method for EOLC patients was the Visual Analog Scale (47.8%), followed by the Behavioral Pain Scale (22.2%). The Sedation-Agitation Scale and the Pain Assessment Behavior Scale were used with equal frequency (13.0% each) (Figure 2).

Pain management strategies in End-of-Life care in the emergency department: Participants were asked, "what approaches do you prefer for managing pain in EOLC patients?" The most frequently preferred pain management strategy in EOLC patients was dose adjustment based on patient characteristics and clinical conditions (25.9%), followed by the use of adjuvant therapy, such as antiemetics for nausea control (25.0%). The administration of opioids and benzodiazepines for symptom relief was also a common approach (24.3%) (Figure 3).

Competence in explaining prognosis in End-of-Life care: Competence in explaining prognosis in EOLC varied among participants. 32.0% rated themselves as very competent; while 9.5% considered themselves completely competent. In contrast, 26.0% reported slight or no competence. Residents reported lower competence levels compared to

Table 1. Factors associated with self-assessed knowledge on EOLC

	Total (n=200)	Completely inadequate (n=28)	Inadequate (n=54)	Undecided (n=91)	Adequate (n=27)	p-value
Age, median (Q1-Q3)	31 (28-37)	31.5 (29-37.75)	30 (28-36)	31 (29-36)	35 (30.75-38.25)	0.027[a]
Gender, n (%)						
Male	107 (53.5)	16 (57.1)	27 (50.0)	53 (58.2)	11 (40.7)	0.391[b]
Female	93 (46.5)	12 (42.9)	27 (50.0)	38 (41.8)	16 (59.3)	
Professional title, n (%)						
Emergency resident	108 (54)	14 (50.0)	37 (68.5)	50 (54.9)	7 (25.9)	0.021[c]
Faculty member	18 (9)	2 (7.1)	3 (5.6)	8 (8.8)	5 (18.5)	
Specialist	74 (37)	12 (42.9)	14 (25.9)	33 (36.3)	15 (55.6)	
Professional experience, n (%)						
<2 years	21 (10.5)	2 (7.1)	12 (22.2)	6 (6.6)	1 (3.7)	0.024[b]
2- ≤5 years	76 (38)	11 (39.3)	18 (33.3)	41 (45.1)	6 (22.2)	
>5-10 years	55 (27.5)	9 (32.1)	14 (25.9)	24 (26.4)	8 (29.6)	
>10 years	48 (24)	6 (21.4)	10 (18.5)	20 (22.0)	12 (44.4)	
EOL training, n (%)						
Yes	29 (14.5)	1 (3.6)	4 (7.4)	9 (9.9)	15 (55.6)	<0.001[c]
No	171 (85.5)	27 (96.4)	50 (92.6)	82 (90.1)	12 (44.4)	

The data are presented as median (Q1-Q3) and n (%). EOL: End-of-life, EOLC: End-of-life care, Q1-Q3: Interquartile range (first and third quartiles). Statistical tests: [a]Kruskal-Wallis test, [b]Chi-square test, [c]Fisher-Freeman-Halton test

faculty members and specialists, with the highest proportion of those rating themselves as completely competent observed among specialists (p=0.005) (Table 2). Additionally, physicians who had received EOLC training were more likely to rate themselves as completely competent (26.3% vs. 9.5%, p=0.048) (Table 2).

Perspectives on the implementation of "do not resuscitate" orders in the emergency department: Participants were asked about the implementation of "do not resuscitate" (DNR) orders for EOLC patients experiencing cardiac arrest in the ED. More than half (54.0%) supported the application of DNR orders, whereas 21.5% opposed their use, and 24.5% remained undecided.

Assessment of organ and tissue donation in End-of-Life care: Participants were asked how often participants consider organ and tissue donation during EOLC. Responses indicated that such considerations were generally infrequent. Specifically, 16.0% reported "never" considering it, 34.5% stated "rarely," 21.5% indicated "occasionally," 19.0% reported "often," and only 9.0% stated they "always" considered it. The frequency of considering organ and tissue donation did not differ significantly across demographic or professional characteristics, including age (p=0.997), gender (p=0.814), professional title (p=0.588), years of experience (p=0.519), or prior EOLC training (p=0.219). A detailed distribution of responses is presented in Figure 4.

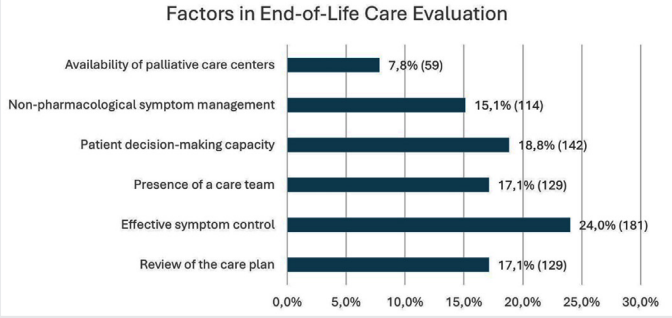

Figure 1. Factors considered in evaluating EOLC in EDs
EOLC: End-of-life care, ED: Emergency department

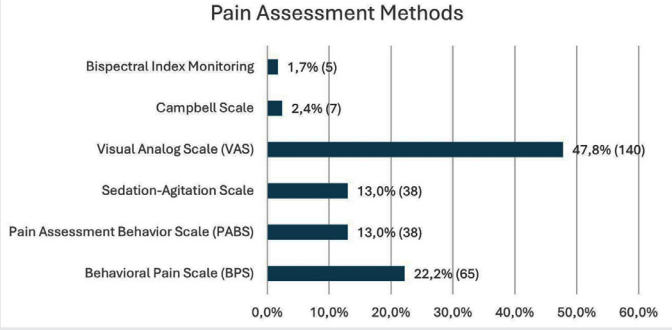

Figure 2. Pain Assessment methods in EOLC
EOLC: End-of-life care

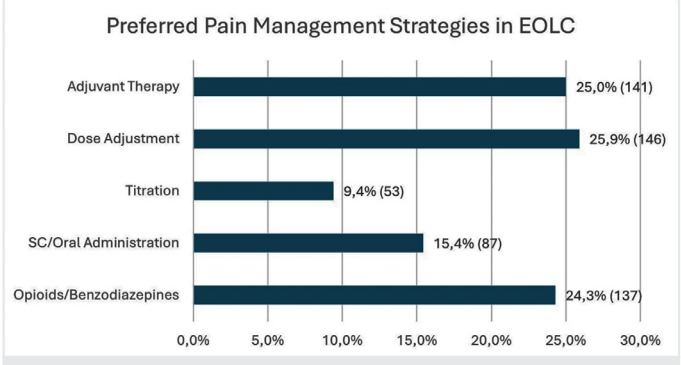

Figure 3. Preferred pain management in EOLC
EOLC: End-of-life care, SC: Subcutaneous

Cultural and spiritual needs: Participants were asked about their perspectives on cultural and spiritual needs in EOLC. The majority of participants (90.0%) agreed or strongly agreed on the importance of ensuring privacy for EOLC patients in the ED. Additionally, 75.0% supported involving the patient's family in decision-making, while 25.0% were either undecided or opposed. Regarding the provision of culturally and religiously appropriate care, only 25.5% expressed agreement, whereas 74.5% were undecided or disagreed (Figure 5). Furthermore, 70.0% supported the establishment of a designated "discussion and farewell" room for grieving families. No significant associations were found between these perspectives and demographic or professional factors, including age, gender, professional title, years of experience, or prior training (p>0.05).

Perspectives on including End-of-Life care education in emergency medicine curricula: Participants were asked about their perspectives on incorporating EOLC education into the emergency medicine curriculum. The majority of participants (76.0%) supported the inclusion of EOLC education in the emergency medicine curriculum, with 40.0% strongly agreeing and 36.0% agreeing. In contrast, 15.0% were undecided, and 9.0% disagreed. No significant differences were observed across demographic or professional characteristics (p>0.05).

Accessibility of specialist team support: Participants were asked, "How would you rate the accessibility of specialist team support when needed for EOLC?" The accessibility of specialist team support for EOLC was rated as inadequate by 58.0% of participants, with 29.5% considering it completely inaccessible and 28.5% as generally not accessible (Figure 6).

Challenges encountered by emergency physicians in managing End-of-Life patients: Participants were asked about the challenges they encounter while managing EOL patients in the ED. The most frequently reported challenges were admission barriers and unrealistic expectations from family members, each cited by 20.3%. A detailed breakdown of reported challenges is illustrated in Figure 7.

Preferred topics for further knowledge in End-of-Life care: Participants were asked about specific topics they wished to learn more about in EOLC. The most frequently selected topic for further knowledge in EOLC was decision-making processes (25.6%), followed by medication management and treatment planning (20.7%) and communication skills with patients and their families (18.8%). Additionally, managing critically ill patients in intensive care units (ICUs) (19.2%) and providing psychological and spiritual support (15.3%) were identified as key areas of interest. A small proportion (0.3%) selected "other," which included topics related to legal procedures.

Preferred training methods in End-of-Life care education: Participants were asked about their preferred training methods for EOLC education. The most preferred method for EOLC education was multidisciplinary training

Table 2. Factors associated with self-perceived competence in communicating prognosis in EOLC

	Total (n=200)	Not at all (n=15)	Slightly (n=37)	Moderately (n=65)	Very (n=64)	Completely (n=19)	p-value
Age, median (Q1-Q3)	31 (24:55)	35 (28-37)	30 (27.5-34)	30 (29-37.5)	32.5 (28-37)	35 (30-40)	0.082[a]
Gender, n (%)							
Male	107 (53.5)	9 (60)	26 (70.3)	31 (47.7)	30 (46.9)	11 (57.9)	0.159[b]
Female	93 (46.5)	6 (40)	11 (29.7)	34 (52.3)	34 (53.1)	8 (42.1)	
Professional title, n (%)							
Emergency resident	108 (54)	6 (40)	28 (75.7)	36 (55.4)	34 (53.1)	4 (21.1)	0.005[c]
Faculty member	18 (9)	1 (6.7)	0	5 (7.7)	7 (10.9)	5 (26.3)	
Specialist	74 (37)	8 (53.8)	9 (24.3)	24 (36.9)	23 (35.9)	10 (52.6)	
Professional experience, n (%)							
<2 years	21 (10.5)	1 (6.7)	7 (18.9)	8 (12.3)	5 (7.8)	0	0.091[c]
2- ≤5 years	76 (38)	4 (26.7)	18 (48.6)	28 (43.1)	22 (34.4)	4 (21.1)	
>5-10 years	55 (27.5)	5 (33.3)	9 (24.3)	13 (20)	19 (29.7)	9 (47.4)	
>10 years	48 (24)	5 (33.3)	3 (8.1)	16 (24.6)	18 (28.1)	6 (31.6)	
EOL training, n (%)							
Yes	29 (14.5)	2 (13.3)	1 (2.7)	14 (21.5)	7 (10.9)	5 (26.3)	0.048[b]
No	171 (85.5)	13 (86.7)	36 (97.3)	51 (78.5)	57 (89.1)	14 (73.7)	

The data are presented as median (Q1-Q3) and n (%). EOL: End-of-life, EOLC: End-of-life care, Q1-Q3: Interquartile range (first and third quartiles). Statistical Tests: [a]Kruskal-Wallis test, [b]Chi-square test, [c]Fisher-Freeman-Halton test

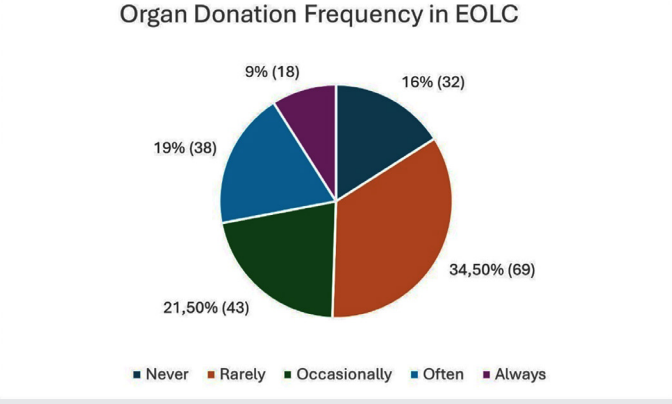

Figure 4. Frequency of organ and tissue donation consideration in EOLC
EOLC: End-of-life care

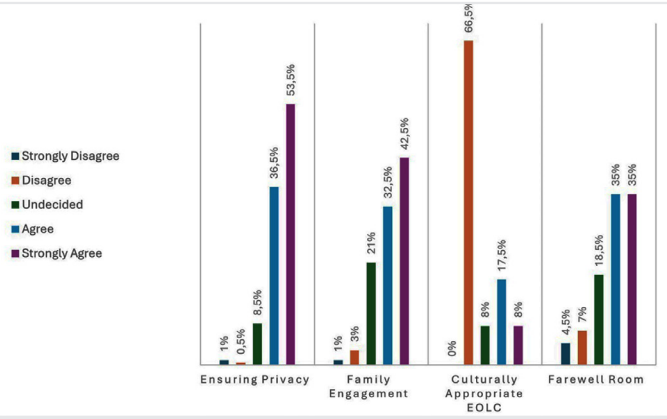

Figure 5. Cultural and spiritual needs in EOLC. Participants' perspectives on cultural care, privacy, family involvement, and farewell rooms.
EOLC: End-of-life care

(32.9%), involving collaboration with professionals such as oncologists, intensivists, psychologists, and family physicians. This was followed by problem-based learning, including case-based scenarios (23.0%), and theoretical education, such as lectures and seminars (16.2%). Online learning tools and digital resources (14.8%) were also selected, while in-service training programs (13.1%) were the least preferred approaches.

Discussion

In this study, we found that emergency physicians generally lack formal training in EOLC, rate their knowledge as inadequate, and face significant systemic barriers in delivering effective care. The majority of participants reported no formal training, with older and more experienced physicians rating their knowledge more favorably, suggesting that age and experience influence perceptions of knowledge adequacy. Similar findings from South Africa and Ireland highlight significant knowledge deficits among younger physicians, largely due to

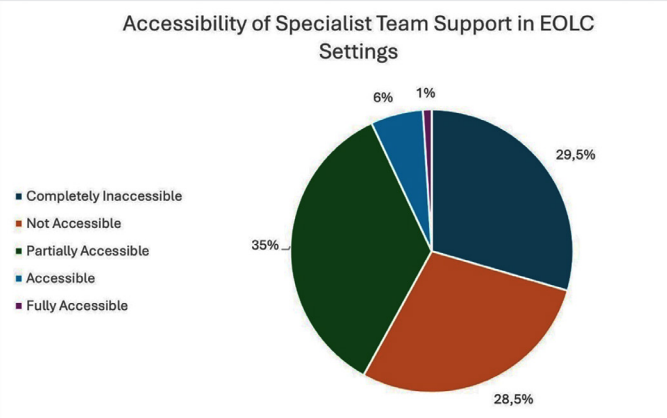

Figure 6. Accessibility of specialist teams in EOLC
EOLC: End-of-life care

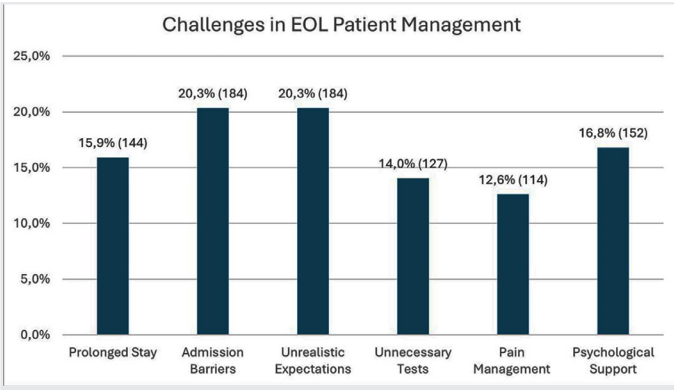

Figure 7. Challenges in managing EOL patients in EDs
EOLC: End-of-life care, ED: Emergency department

limited training opportunities (17,18). Physicians who received formal EOLC training in our study reported greater confidence in explaining patient prognosis, aligning with evidence that training reduces role ambiguity and improves communication skills (18).

Existing literature underscores the importance of practical models and skills-based approaches in EOLC training (14,15). For example, a New York study found that emergency medicine residents recognized the value of palliative care but had received limited formal training (19). Similarly, despite EOLC being included in the ABEM curriculum, critical areas such as symptom management, care during the dying process, and hospice patient management remain inadequately addressed (20). Research from Canada further emphasizes that EOLC training often consists of theoretical lectures, lacking practical application (21). Participants in our study expressed strong agreement about the need to integrate EOLC training into curricula and showed a preference for scenario-based, multidisciplinary approaches.

Participants identified key challenges in EOLC, including insufficient support from specialized teams, prolonged waiting times, admission barriers, and inadequate psychological resources. Integrating palliative care services into EDs has the potential to enhance patient outcomes; however, systemic barriers such as resource shortages and a lack of trained staff remain significant obstacles (22,23). Multidisciplinary collaboration and improved environments are crucial to addressing these challenges (24). A qualitative study further emphasized that communication gaps, uncertainties, and conflicts at the ED-ICU interface could negatively impact EOLC decisions, particularly for elderly and critically ill patients (25). These findings highlight the need to strengthen communication processes and foster collaboration to address existing challenges in EOLC delivery within emergency settings.

Effective symptom control was identified in our study as one of the most frequently cited critical factors in the evaluation of EOL patients. This finding aligns with research defining quality indicators in EOLC, which emphasizes symptom management as a fundamental domain (26). Additionally, 75% of participants supported involving families in decision-making processes, consistent with literature highlighting the importance of patient- and family-centered care (27). Participants preferred dose adjustments based on patient characteristics and the use of opioids and benzodiazepines for symptom control in EOL patients. The literature highlights the widespread use of medications such as morphine and midazolam during the withdrawal of life-sustaining treatments, often with dose escalation (28). A systematic review underscores the importance of quantitative tools for pain assessment, high-dose opioids, and decisions guided by ethical principles (29). Consistent with this, participants in our study commonly used the VAS for pain assessment, reflecting its practical application in EOL care.

DNR orders remain a contentious issue, with 54% of participants favoring implementation, while 24.5% remain undecided, likely due to the absence of a legal framework for DNR practices in Türkiye. The literature emphasizes evaluating DNR decisions within the context of patient autonomy and ethical principles, noting that cultural and religious values can significantly influence these processes (10,30). Finally, participants emphasized the importance of privacy and physical arrangements, such as farewell rooms, in delivering respectful and compassionate care. Quiet spaces in EDs not only support families but also aid healthcare professionals in managing sensitive EOL processes (8,10,24).

Our study identified significant gaps in emergency physicians' knowledge and training in EOLC, alongside systemic barriers that hinder the delivery of effective care. Future studies may explore the impact of structured training programs and assess the feasibility of integrated palliative care models in EDs, offering valuable insights to advance EOLC practices.

Study Limitations

This study has several limitations. It is a cross-sectional survey, capturing only a snapshot of participants' knowledge, attitudes, and experiences. Self-reported data may not fully reflect actual practices or competencies; and non-response bias was not assessed, which may affect the generalizability of the findings. Additionally, the response rate was 48%, which may introduce selection bias and limit the representativeness of the sample.

Conclusions

This study reveals significant gaps in emergency physicians' self-assessed knowledge and training related to EOLC, with younger and less experienced physicians being most affected. Limited access to specialist team support and challenges such as prolonged ED stays were frequently highlighted by participants. These findings indicate the need for enhanced educational initiatives, better resource allocation, and systemic improvements to effectively address the multifaceted challenges associated with EOLC in emergency care settings.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of İstanbul Medipol University (approval number: 919, date: 26.04.2024).

Informed Consent: Actively working emergency medicine residents, specialists, and faculty members (assistant professors, associate

professors, and professors) who provided electronic or written informed consent and completed the survey in full were recruited for the study.

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Footnotes

Authorship Contributions: Concept - M.E., B.A.K., E.Ü.A.; Design - M.E., B.A.K., E.Ü.A.; Data Collection or Processing - M.E., B.A.K.; Analysis or Interpretation - M.E., E.Ü.A.; Literature Search - M.E., B.A.K., E.Ü.A.; Writing - M.E., B.A.K., E.Ü.A.

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

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The Role of MR-proADM in Determining COVID-19 Pneumonia and Clinical Severity

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ABSTRACT

Introduction: This study aimed to compare the success of mid-regional pro adrenomedullin (Mr-proADM) levels, in determining disease severity in coronavirus disease-2019 (COVID-19) patients with other inflammatory biomarkers and Pneumonia Severity Index (PSI) scores.

Methods: This prospective, observational, analytical, cross-sectional study was conducted at Sakarya Training and Research Hospital, Department of Emergency Medicine. The 88 patients who presented with suspected COVID-19 and were diagnosed accordingly were included in the examination. The patients were organized into four groups based on reverse transcription polymerase chain reaction and chest computed tomography outcomes. Demographic data, presenting complaints, comorbidities, laboratory values, imaging modalities, PSI score, and pneumonia diagnosis data were documented for each patient. All data were examined with SPSS software, and a $p<0.05$ was considered statistically significant.

Results: The patients' mean age was 53 and 60% were female. Fatigue (58%) was the most typical complaint, and hypertension (39%) was the most prevalent comorbidity. When comparing the groups, it was observed that patients in group 4 exhibited a decrease in white blood cell counts and increased levels of C-reactive protein (CRP), ferritin, and D-dimer, which was statistically significant. Nevertheless, no significant distinction was seen in Mr-proADM levels among the groups. The comparison based on the PSI score determined that Mr-proADM levels were significantly raised in the high-risk group.

Conclusion: Mr-proADM levels correlated with CRP, ferritin, and procalcitonin levels in predicting patients in the high-risk group based on the PSI score. Based on these determinations, Mr-proADM levels may also help predict clinical severity in the emergency department. Nevertheless, further studies incorporating larger datasets are needed to support these data.

Keywords: Emergency department, COVID-19, Mr-proADM, PSI

Introduction

Coronavirus disease-2019 (COVID-19), which emerged in China in late 2019 and affected the entire world, has caused significant challenges in clinical management. In diagnostic approaches, detecting severe acute respiratory syndrome coronavirus-2 in respiratory specimens and characteristic lung infiltrations on chest computed tomography (CT) scans has been used for definitive diagnosis (1). Although not specific, certain laboratory parameters (such as leukocyte, lymphocyte, and platelet counts), biochemical analyses (such as ferritin levels, troponins, and renal function tests), serological tests [such as D-dimer, C-reactive protein (CRP), and procalcitonin], and arterial blood gas analysis (such as lactate) have been recommended to support the diagnosis in suspected cases (2).

Additionally, the need to assess pneumonia, which is frequently observed in COVID-19 patients, has emerged. In this context, the Pneumonia Severity Index (PSI) scoring system has gained prominence (1,3). According to the PSI scoring system, grades 1-3 indicate mild disease, whereas grades 4-5 classify cases as severe, implying a higher risk of mortality and an increased need for hospitalization (4).

The PSI score considers various parameters associated with an elevated risk of mortality in COVID-19 patients, such as age, comorbidities, and hypoxemia (1,3). However, despite these approaches, there remains a demand for novel diagnostic mechanisms because of limitations in certain patients and the persistently high mortality rate. One emerging biomarker in this context is mid-regional pro adrenomedullin (MR-proADM) (5).

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MR-proADM is a polypeptide with multiple physiological effects, including vasodilation, natriuresis, diuresis, antioxidation, antimicrobial activity, anti-inflammatory properties, and metabolic regulation. It is produced by endothelial cells in cardiovascular, pulmonary, cerebrovascular, renal, and endocrine tissues (5). Given these characteristics, studies have suggested that MR-proADM can be used for diagnosis, monitoring, and prognosis in bacterial infections such as pneumonia and sepsis. However, there is currently insufficient evidence regarding its effectiveness in viral infections (6). The literature provides limited information on the relationship between MR-proADM and COVID-19 (7).

This study aims to investigate the contribution of MR-proADM to the diagnostic process and its effectiveness in assessing disease severity in patients presenting with COVID-19 symptoms in the emergency department (ED) by comparing MR-proADM with other inflammatory biomarkers and the PSI score.

Methods

Study Type

This prospective, observational, analytical, cross-sectional study included patients who presented with COVID-19 symptoms at Sakarya Training and Research Hospital (SEAH) ED and underwent MR-proADM testing.

Study Design

The study was conducted between May 4 and November 4, 2020, with 88 patients presenting COVID-19 symptoms at SEAH ED. Patients were classified into four subgroups based on reverse transcription polymerase chain reaction (RT-PCR) and thoracic CT findings:

Group 1: RT-PCR negative, CT pneumonia negative

Group 2: RT-PCR positive, CT pneumonia negative

Group 3: RT-PCR negative, CT pneumonia positive

Group 4: RT-PCR positive, CT pneumonia positive

MR-proADM testing was performed alongside routine laboratory tests. Patients were assigned to groups based on the researchers' shifts in the ED, and recruitment ceased once each group reached the specified sample size.

The study was approved by the Non-Interventional Clinical Research Ethics Committee of Sakarya University (approval number: 212, date: 20.04.2020). Written informed consent was obtained from all participants. The study adhered to the 2004 World Medical Association Declaration of Helsinki.

Diagnosis

RT-PCR testing was conducted on both nasopharyngeal and oral swab samples. Thoracic CT images were classified as CT pneumonia positive if CO-RADS scores were 4 or 5 (8).

Data Collection

Patient data were obtained from the hospital automation system and recorded on a structured study form. The collected data included:

- Demographics (age, gender)
- Presenting complaints and comorbidities
- Vital parameters (blood pressure, pulse rate, temperature, respiratory rate, peripheral oxygen saturation)
- Laboratory results [RT-PCR, white blood cell (WBC), CRP, procalcitonin, troponin, ferritin, D-Dimer, Lactate, MR-proADM]
- Thoracic CT results and PSI scores

Inclusion criteria: Patients 18 and older with COVID-19 symptoms undergoing MR-proADM testing.

Exclusion criteria: Pregnant patients and those with missing study-relevant data.

Statistical Analysis

Normal distribution was assessed using Skewness-Kurtosis values (-2 to +2 range) and the Kolmogorov-Smirnov test (9). Non-normally distributed continuous variables were reported as median interquartile range values. Statistical tests included:

- **Mann-Whitney U test**: Comparison between two groups
- **Kruskal-Wallis test**: Comparison among four groups, with posthoc pairwise comparisons using the Mann-Whitney U test
- **Chi-square test**: Analysis of categorical variables among groups

A $p<0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics 21.

Results

Of the patients participating in the study, 60% were female, with a mean age of 53.3 years (range: 18-90). Fatigue (58%) and fever (55.7%) were the most common presenting complaints. A statistically significant difference was observed between the groups in terms of age. In subgroup analyses, statistically significant differences were found between Group 2 and Group 3, as well as between Group 2 and Group 4 ($p=0.035$ and $p=0.009$, respectively).

Regarding symptoms, statistically significant differences were observed among the groups for fever, shortness of breath, and fatigue ($p=0.036$, $p=0.004$, $p=0.003$, respectively). Subgroup analyses revealed a statistically significant difference in fever between Group 2 and Group 3 ($p=0.004$). Regarding shortness of breath, a statistically significant difference was found between Group 1 and Group 2 ($p=0.004$). Additionally, subgroup analyses showed significant differences in malaise between Group 1 and Group 2, as well as between Group 2 and Group 3 ($p=0.003$, $p=0.001$, respectively). While the most common symptoms in Group 4 were fever and fatigue, shortness of breath was predominant in Group 1. Hypertension was the most frequently observed comorbidity (Table 1).

Among the study participants, 43.2% were discharged from the ED, 48.8% were admitted to a standard hospital room, and 8% required admission to the intensive care unit (ICU). Statistically significant differences were observed between the groups regarding discharge rates and standard

Table 1. Demographic datas, admission complaints and comorbidity

		Total n=88	Group 1 n=20	Group 2 n=20	Group 3 n=20	Group 4 n=28	p
Age, years (min.-max.)		53.30 (18-90)	48.10 (20-80)	44.15 (18-88)[a,b]	59.35 (21-90)[a]	59.21 (40-88)[b]	**0.032***
Gender, female (%)		53 (60,2)	13 (65)	14 (70)	8 (40)	18 (64.3)	0.608**
Admission complaint n (%)	Fever	**49 (55.7)**	10 (50)	16 (80)[a]	7 (35)[a]	**16 (57.1)**	**0.036****
	Cough	42 (47.7)	13 (65)	9 (45)	9 (45)	11 (39.3)	0.346**
	Sore throat	25 (28.4)	9 (45)	5 (25)	5 (25)	6 (21.4)	0.307**
	Shortness of breath	30 (34.1)	**12 (60)[a]**	2 (10)[a]	9 (45)	7 (25)	**0.004****
	Muscle/joint pain	29 (33.0)	7 (35)	9 (45)	5 (25)	8 (28.6)	0.538**
	Resentment	**51 (58.0)**	8 (40)[a]	17 (85)[a,b]	7 (35)[b]	**19 (67.9)**	**0.003****
	Abdominal pain/diarrhea	10 (11.4)	1 (5)	3 (15)	4 (20)	2 (7.1)	0.385**
Comorbidity n (%)	Diabetes mellitus	23 (26.1)	3 (15)	6 (30)	5 (25)	9 (32.1)	0.261**
	Hypertension	**34 (38.6)**	8 (40)	5 (25)	8 (40)	**13 (46.4)**	0.409**
	Cardiovascular disease	16 (18.2)	3 (15)	2 (10)	5 (25)	6 (21.4)	0.362**
	Chronic lung disease	7 (8.0)	1 (5)	1 (5)	2 (10)	3 (10.7)	0.386**
Outcome n (%)	Discharge	38 (43.2)	**19 (95)[a,b]**	15 (75)[c,d]	3 (15)[a,c]	1 (3.6)[b,d]	**0.000****
	Standart room	43 (48.8)	1 (5)[a,b]	5 (25)[c]	13 (65)[a]	**24 (85.7)[b,c]**	**0.000****
	Intensive care unit	7 (8)	0 (0)	0 (0)	4 (20)	3 (10.7)	0.054**

*The Kruskal Wallis test is used for 4 group analyses. **Chi-square test is used for analysis. [a,b,c,d] There is no significant difference between the groups indicated with the same letter in the same row. Min.: Minimum, Max.: Maximum

room admissions (p=0.000, p=0.000, respectively). Subgroup analyses, showed statistically significant differences in discharge rates between Group 1 and Group 3, Group 1 and Group 4, Group 2 and Group 3, and Group 2 and Group 4 (p=0.000 for all comparisons). Similarly, subgroup analyses of standard room admissions revealed significant differences between Group 1 and Group 3, Group 1 and Group 4, and Group 2 and Group 4 (p=0.000 for all comparisons) (Table 1).

Laboratory data are presented in Table 2. No significant differences were found in procalcitonin, lactate, or Mr-proADM levels (p=0.061, p=0.601, p=0.151, respectively). However, significant differences were observed among the groups for WBC, CRP, ferritin, troponin, and D-dimer levels: p=0.001; p=0.002; p=0.000; p=0.025; p=0.029, respectively. In subgroup analyses of WBC levels, statistically significant differences were noted between Group 1 and Group 2, as well as between Group 1 and Group 4 (p=0.014, p=0.000, respectively). For CRP values, a significant difference was found between Group 2 and Group 3 (p=0.029). Regarding ferritin levels, subgroup analyses revealed significant differences between Group 1 and Group 3 (p=0.028), Group 1 and Group 4 (p=0.010), and between Group 2 and Group 3 (p=0.019), Group 2 and Group 4 (p=0.007). In subgroup analyses of troponin levels, significant differences were found between Group 2 and Group 3, as well as between Group 2 and Group 4 (p=0.005, p=0.026, respectively). Subgroup analyses of D-Dimer levels showed significant differences between Group 2 and Group 3, as well as between Group 3 and Group 4 (p=0.003, p=0.036, respectively).

Based on the PSI score, Mr-proADM levels were significantly higher in the high-risk group compared to the low-risk group (p=0.008). Additionally, in the high-risk group, Mr-proADM levels was correlated with increased levels of CRP, ferritin, and procalcitonin (p=0.003, p=0.000, p=0.001, respectively) (Table 3).

Table 2. Laboratory values of the groups

	Reference value	Total n=88	Group 1 n=20	Group 2 n=20	Group 3 n=20	Group 4 n=28	p
WBC	4.60-10.20 K/uL (IQR)	6.96 (5.22-9.52)	10.12 (7.69-12.12)[a,b]	6.24 (5.35-8.52)[a]	6.84 (4.86-10.61)	**5.72 (5.06-7.52)[b]**	**0.001***
CRP	0-5 mg/L (IQR)	11.15 (4.22-32.55)	8.09 (0.85-24.08)	5.98 (1.87-10.58)[a]	15.15 (6.40-78.05)[a]	**18.33 (7.72-59.97)**	**0.002***
Prokalsitonin	<0.5 ng/mL (IQR)	0.04 (0.02-0.07)	0.04 (0.02-0.06)	0.03 (0.02-0.06)	0.05 (0.04-0.83)	0.04 (0.02-0.08)	0.063*
Ferritin	21.8-274.6 µg/L (IQR)	90.92 (30.31-203.41)	55.39 (14.67-97.39)[a,b]	30.31 (20.20-70.20)[c,d]	135.05 (85.22-250.67)[a,c]	**202.55 (82.52-339.26)[b,d]**	**0.000***
Troponin	0-34.2 ng/L (IQR)	2.40 (0.65-6.10)	1.30 (0.52-5.37)	0.85 (0.25-3.47)[a,b]	**4.70 (1.32-4.70)[a]**	3.20 (1.27-6.60)[b]	**0.025***
D-Dimer	0-500 ugFEU/L (IQR)	400.0 (208.0-814.0)	311.0 (189.0-1003.25)	314.0 (176.25-488.00)[a]	**736.0 (350.0-2615.0)[a,b]**	379.50 (197.25-693.25)[b]	**0.029***
Laktat	0.5-1.6 mmol/L (IQR)	1.50 (1.20-1.90)	1.40 (1.12-1.87)	1.40 (1.12-1.87)	1.65 (1.32-1.90)	1.55 (1.22-1.87)	0.601*
Mr-proADM	pmol/mL (IQR)	0.54 (0.39-1.26)	0.88 (0.43-3.25)	0.45 (0.37-1.68)	0.68 (0.36-1.32)	0.53 (0.37-0.94)	0.151*

*Kruskal Wallis test is used for 4 group analyse. The Mann-Whitney U test is used for subgroup analysis. [a,b,c,d] There is a significant difference between the groups indicated with the same letter in the same row. WBC: White blood cell, CRP: C-reactive protein, IQR: Interquartile range, Mr-proADM: Mid-regional pro adrenomedullin

Table 3. Laboratory values according to the PSI results

	PSI (1-3) low-risk n=73	PSI (4-5) high-risk n=15	p-value
WBC 4.60-10.20 K/uL (min.-max.)	7.65 (2.56-14.99)	7.70 (3.32-17.70)	0.829*
CRP 0-5 mg/L (min.-max.)	27.01 (0.21-333.80)	**44.46 (9.40-136.00)**	**0.003***
Prokalsitonin <0.5 ng/mL (min.-max.)	0.15 (0.01-3.50)	**1.16 (0.02-15.10)**	**0.000***
Ferritin 21.8-274.6 µg/L (min.-max.)	116.52 (1.80-697.00)	**351.44 (16.88-1248.40)**	**0.001***
Laktat 0.5-1.6 mmol/L (min.-max.)	1.59 (0.70-4.10)	1.69 (0.80-4.20)	0.807*
Mr-proADM (pmol/mL) (min.-max.)	1.31 (0.34-13.97)	**2.54 (0.34-25.37)**	**0.008***

*Mann Whitbey U test is usedfor analyse.WBC: White blood cell, CRP: C-reactive protein, PSI: Pneumonia severity index, Mr-proADM: Mid-regional pro adrenomedullin, Min.: Minimum, Max.: Maximum

Discussion

According to this study, patients who presented to the ED due to COVID-19 exhibited symptoms such as fever, shortness of breath, and fatigue. In the group analysis of laboratory data, significant differences were observed in WBC, CRP, ferritin, troponin, and D-dimer levels. At the same time, no distinctions were observed in procalcitonin, lactate, and Mr-proADM levels. The levels of Mr-proADM do not provide an additional contribution to the diagnostic process. However, the levels of Mr-proADM, CRP, ferritin, and procalcitonin, which are correlated with Mr-proADM levels, can predict the high-risk group according to the PSI scoring system.

A review of the literature indicates that numerous symptoms have been identified as reasons for hospitalization in COVID-19 patients. However, the most commonly reported symptoms include fever, cough, and fatigue (10-12). Given that COVID-19 is a viral infection, the prominence of fever and fatigue is expected. In our study, the highest incidence of fever and fatigue was observed in RT-PCR and CT pneumonia-positive patients (Group 4), which aligns with the literature. However, it is noteworthy that shortness of breath was more prominent in RT-PCR and CT pneumonia-negative patients (Group 1), which contrasts with previous findings.

Extensive studies on laboratory parameters in COVID-19 patients have highlighted WBC, CRP, ferritin, troponin, D-dimer, and procalcitonin as key indicators. Generally, a normal WBC count is expected, whereas elevated CRP and Ferritin levels are associated with disease severity and poor prognosis. Studies have reported increased CRP levels in 55-85% of patients and elevated ferritin levels in 90.7% of cases (12-18). In our study, although significant differences were observed among groups in WBC counts and ferritin levels, the values remained within the reference range, aligning with existing literature. Similarly, the elevated CRP levels observed in our study are consistent with previous findings.

Several publications suggest a positive correlation between COVID-19 severity and cardiac involvement; this leads to increased troponin levels, a classic marker of myocardial injury. However, studies indicate that elevated Troponin levels are more closely associated with inflammatory markers such as CRP and Ferritin, suggesting that the increase is due to inflammatory damage rather than primary myocardial injury (19-22). Additionally, research has shown that elevated D-dimer levels in COVID-19 patients result from disease-related coagulopathy, with high serum levels indicating thromboembolic risk. Elevated D-dimer levels are more frequently observed in severe COVID-19 cases, and an increase beyond 1 mcg/mL has been associated with poor prognosis (23,24). Procalcitonin levels, on the other hand, generally remain within normal limits in COVID-19 patients, with elevated levels potentially indicating bacterial superinfection (25,26). In our study, we found that D-dimer levels exceeded the reference range, only in RT-PCR-negative and CT pneumonia-positive patients (Group 3), while no significant subgroup differences were observed in troponin levels. This result may be attributed to differences in the patient population. Additionally, our Procalcitonin findings remained within normal limits supporting the existing literature.

Many studies have attempted to develop predictive models for assessing COVID-19 severity. Previous research has identified PCT, CRP, ferritin, and lymphocyte count as biomarkers associated with severe disease. However, the comparative discriminatory ability of these biomarkers has not been extensively studied. The widely used PSI score has demonstrated strong performance in comparison with these biomarkers (27,28). One commonly used inflammatory marker in ED patients with suspected infection is MR-proADM. A study on this topic suggested that MR-proADM levels below 0.9 nmol/L may indicate a lower likelihood of hospitalization and re-presentation, whereas levels above 1.5 nmol/L may suggest severe and progressive disease, emphasizing the importance of early antibiotic treatment (29). Another study on COVID-19 reported that high MR-proADM levels were associated with ICU admission and mortality (7). In our study, the mean MR-proADM levels were found to be approximately 0.54 nmol/L, which is below the <0.9 nmol/L threshold reported in the literature. This finding suggests that the patients included in our study had milder cases of COVID-19, which explains why only 8% required ICU admission. Furthermore, the lack of significant differences among patient groups suggests that MR-proADM levels do not provide additional diagnostic value. However, another study on pneumonia-one of the most common clinical presentations of COVID-19-reported a positive correlation between MR-proADM levels and severity assessed by the PSI score. Our study also identified a positive correlation with the PSI severity score, suggesting that MR-proADM levels could serve as an indicator of clinical severity and hospitalization requirements in COVID-19 patients with pneumonia.

Study Limitations

The primary limitations of this study include its single-center design and limited sample size. Additionally, as a cross-sectional study, it did not comprehensively assess patient prognosis. Another limitation is the lack of randomization, as data collection was restricted to the authors' ED shifts.

Conclusion

MR-proADM levels do not provide additional diagnostic value in predicting RT-PCR or CT scan results in COVID-19 patients. However, the PSI score demonstrates a correlation of CRP, Ferritin, and Procalcitonin levels with identifying high-risk patients. Based on these findings, MR-proADM levels may serve as an indicator of clinical severity in the ED. Nonetheless, further studies with larger datasets are necessary to validate these findings.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Sakarya University (approval number: 212, date: 20.04.2020).

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

Footnotes

Authorship Contributions: Concept - S.A., Y.Y., N.G.G., N.A., F.G.; Design - S.A., Y.Y., H.Y., N.G.G., N.A., F.G.; Data Collection or Processing - S.A., N.G.G., N.A., E.D.; Analysis or Interpretation - S.A., H.Y., N.G.G., E.D., F.G.; Literature Search - S.A., Y.Y., H.Y., N.A.; Writing - S.A., Y.Y., E.D., F.G.

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Polymyalgia Rheumatica: Clinical Features and Third Month Treatment Responses-A Single-Center Experience

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ABSTRACT

Introduction: This study aimed to evaluate the clinical features, comorbidities, and third month treatment responses of polymyalgia rheumatica (PMR) patients followed in a single rheumatology unit.

Methods: Thirteen patients diagnosed with PMR based on the 2012 European League Against Rheumatism/American College of Rheumatology Classification Criteria were retrospectively analyzed. Baseline demographics, clinical, and laboratory findings, positron emission tomography-computed tomography (PET-CT) results, and treatment responses at the third month were reviewed.

Results: A total of 13 patients (3 male/10 female) were included in the present study. The mean age of the cohort was 76±7.3 years, with a female predominance (76%). Morning stiffness was the most frequent symptom (100%), followed by shoulder pain (92%) and groin pain (38%). PET-CT revealed periarticular F-fluorodeoxyglucose uptake in 92% of cases, with no evidence of vasculitis. Prednisolone therapy was initiated in all patients, and significant symptom relief, and reductions in C-reactive protein levels were observed by the third month (p=0.02).

Conclusion: PMR frequently overlaps with other conditions, complicating its diagnosis. PET-CT can be a valuable tool in identifying periarticular inflammation but remains limited by its cost. Prednisolone therapy was effective in achieving rapid symptom relief, although clinicians must remain cautious about its long-term adverse effects, particularly in geriatric populations.

Keywords: Polymyalgia rheumatica, PET-CT, vasculitis

Introduction

Polymyalgia rheumatica (PMR) is a relatively common rheumatic condition in the elderly population (1). PMR predominantly affects individuals over 50, with the highest incidence occurring between the ages of 70 and 80 (2). Despite its high prevalence in elderly populations, the exact etiology of PMR remains unclear, while activation of innate and adaptive immune systems in response to unknown environmental triggers appears to be a plausible pathogenesis (3).

PMR is typically diagnosed based on clinical presentation, supported by elevated inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein (CRP) (4). However, its diagnosis can be challenging due to the absence of specific diagnostic tests and its clinical similarities with other inflammatory and non-inflammatory conditions, such as myositis, seronegative rheumatoid arthritis, calcium pyrophosphate disease, frozen shoulder, fibromyalgia, spondylosis, osteoarthritis, and even malignancies (5,6). These overlapping features frequently lead to delayed diagnosis, which in turn prolongs patient suffering and may lead to unnecessary investigations or inappropriate treatments.

PMR frequently coexists with giant cell arteritis (GCA), another inflammatory condition that primarily affects large and medium-sized arteries. Studies suggest that approximately 20% of PMR patients may develop GCA, and up to 40-50% of GCA patients present with PMR-like symptoms (7-9). However, PMR can also occur as an isolated condition without any vascular involvement. This variability highlights the importance of distinguishing between isolated PMR and cases complicated by GCA, as the latter requires more aggressive monitoring and treatment to prevent severe vascular complications of the large-vessel vasculitis (10).

Recent advancements in imaging modalities have provided a better understanding of the disease's possible organ involvements. Ultrasound is widely used to detect subdeltoid bursitis, biceps tenosynovitis, and hip synovitis, which are characteristic of the disease (11,12). Moreover, fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) has emerged as a powerful tool to identify inflammatory changes in extra-articular sites, including both vascular and periarticular structures (13,14).

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Corticosteroids remain the cornerstone of PMR treatment, providing rapid symptomatic relief (4). However, long-term steroid use is associated with considerable side effects, necessitating a careful balance between disease control and minimizing treatment-related complications.

This study was evaluated presentation characteristics, PET-CT findings and treatment responses of the therapy at the 3rd month of the PMR patients followed in a single rheumatology unit.

Methods

Study Participants

Potential patients were identified between December 2021 and November 2023 through an electronic medical record search of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital using the International Classification of Diseases-10 (ICD-10) code for PMR (M35.3). The study population was identified through a review of patient records using the ICD-10 code for PMR (M35.3). Inclusion criteria required fulfilling the 2012 European League Against Rheumatism/American College of Rheumatology Classification Criteria for PMR (15). Clinical features at presentation and PET/CT findings were retrieved from the electronic medical records. Patients were reevaluated three months after the therapy began. There were no exclusion criteria for the present study. The study was conducted in full compliance with the principles outlined in the Declaration of Helsinki, and it was conducted after obtaining approval from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 267, date: 13.10.2023).

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to assess the normality of data distribution. Continuous variables are presented as mean ± standard deviation (SD) if they follow a normal distribution and as median [interquartile range (IQR)] if they do not. Categorical variables are presented as percentages. Group comparisons were conducted using either the paired sample t-test or the Wilcoxon test, based on the data distribution. The McNemar test was employed for analyzing categorical variables. A p-value of <0.05 was considered statistically significant.

Results

A total of 13 patients (3 male/10 female) were included in the present study. The mean age at diagnosis was 76±7.3 years. The baseline demographics, clinical, and laboratory findings at presentation are presented in Table 1.

Clinical and Laboratory Characteristics and Comorbid Conditions

All the 13 patients (100%) described morning stiffness, which was the most common complaint. Twelve (92% out of the cohort) patients had shoulder pain. Five patients (38%) had groin pain. Five (38%) of the 13 patients had peripheral arthralgia while three (23%) of these had arthritis. None of the patients described any previous headache.

One patient (7%) had a positive rheumatoid factor test, which was 22 IU/l (normal <14 IU/l). None of the patients had anti-cyclic citrullinated peptides test positivity. Five cases had a positive antinuclear antibodies test; however, four of them were borderline positive, and the remaining

Table 1. Baseline demographics, comorbidies, clinical and laboratory findings of the PMR patients

Age of diagnosis, years, mean ± SD	76±7.3
Male, n (%)	3 (24)
Female, n (%)	10 (76)
Comorbidity, n (%) Hypertension Diabetes Coronary heart disease Osteoporosis Solid organ malignancy Monoclonal gammopathy of undetermined significance	 11 (85) 3 (23) 3 (23) 5 (38) 1 (8) 1 (8)
Stiffness, n (%)	13 (100)
Shoulder pain, n (%)	12 (92)
Groin pain, n (%)	5 (38)
Peripheral arthralgia, n (%)	5 (38)
Peripheral arthritis, n (%)	3 (23)
Headache, n (%)	0 (0)
RF positive cases, n (%)	1 (7)
Anti-CCP positive cases, n (%)	0 (0)
ANA positive cases, n (%)	5 (38)
CRP, mg/L, median (IQR)	26.5 (16-47.25)
Sedimentation, mm/h, median (IQR)	64 (37-92.5)

SD: Standard deviation, RF: Rheumatoid factor, Anti-CCP: Anti-Cyclic citrullinated peptides, ANA: Antinuclear antibodies CRP: C-reactive protein, IQR: Interquartile range, PMR: Polymyalgia rheumatica

patient had a 1/160 homogeneous pattern. The median (IQR) sedimentation and CRP levels were 64 (37-92.5) mm/h and 26.5 (16-47.25) mg/L, respectively.

Hypertension and diabetes were observed at the time of PMR diagnosis in 11 (85%) and 3 (23%) patients, respectively. Three (23%) patients had coronary heart disease. Five patients (38%) had osteoporosis. One patient (8%) had previous breast cancer, and another (8%) had monoclonal gammopathy of undetermined significance before PMR diagnosis.

Positron Emission Tomography-Computed Tomography Findings and Clinical Correlation

Twelve (92%) of the 13 patients had periarticular F-fluorodeoxyglucose (FDG) uptake in a PET-CT scan. None of the patients had subclinical large vessel involvement. Of the five patients who presented with peripheral arthralgia, three (60%) had periarticular FDG uptake at peripheral joints. The remaining two patients had no uptake at peripheral joints. Additionally, one of these remaining two patients had wrist arthritis. PET-CT characteristics of the PMR patients were presented in Table 2.

Treatment Responses

Except for one patient, all others were treated with prednisolone. The remaining patient (patient number: 6 in Table 2) with previous breast cancer presented with PMR complaints, and she was diagnosed with a relapse of the breast cancer and PMR. She was treated with paclitaxel and trastuzumab. The mean ± SD prednisolone was 14.5±1.5 mg/day for the remaining patients.

At the end of the 3rd month of the therapy, only two patients still had PMR-related complaints (p=0.01). The median (IQR) CRP level dropped significantly at the control visit [26.5 (16-47.25) mg/L vs. 5 (2.5-9.5) mg/L, p=0.01]. The mean ± SD prednisolone dose was lowered from 14.5±1.5 mg/day to 4.5±2.9 mg/day at 3rd month of the treatment (p=0.0001). None of the patients was treated with additional immunosuppressants except prednisolone. The Treatment responses and prednisolone doses at the 3rd month of the therapy are depicted in Table 3.

Discussion

PMR is increasingly becoming a condition that clinicians encounter, particularly with the aging population. The absence of a diagnostic serological test, coupled with the overlap with other seronegative arthritides and age-related degenerative joint diseases, often leads to diagnostic delays.

Radiological imaging plays a crucial role in diagnosing PMR. Ultrasound stands out as a practical, cost-effective, and safe method. It is highly effective in detecting underlying extra-articular soft tissue involvement, with bursitis and tenosynovitis being the most common findings (11,12). Although MRI is also successful in identifying extra-articular involvement, its high cost limits its routine use (16). PET-CT, while not yet recommended for all suspected cases, has shown significant utility in detecting both extra-articular and potential vascular involvement (13,14). In a study by Blockmans et al. (17), subclinical vasculitis was identified in approximately one-third of patients using PET-CT. One of the factors influencing the success of imaging techniques is prior steroid use, which can reduce the accuracy of imaging findings (18). In our study, none of the patients received steroid treatment before imaging, and PET-CT positivity was detected in 92% of the cases (12 out of 13 patients). No subclinical vasculitis was observed. There are scant data from Türkiye, specifically investigating PET-CT involvement in PMR patients, whereas two recent papers have examined this in GCA. Both studies reported vasculitis in approximately 80% of patients (19,20).

Prednisolone is a highly effective treatment modality for PMR. All patients in our study responded to prednisolone treatment by the third month, reporting no PMR-related symptoms. Despite its effectiveness, clinicians must remain vigilant about the long-term side effects of steroid use. As PMR is more prevalent in the geriatric population, this group is particularly vulnerable to potential adverse effects. In our cohort, comorbidities such as hypertension and osteoporosis, which can be exacerbated by steroid therapy, were present in 85% and 38% of patients, respectively. The literature also supports increased risks of hypertension, osteoporosis, and glaucoma in PMR patients undergoing

Table 2. Clinical and PET-CT characteristics of the PMR patients

Patient number	Age (years)	Sex	Shoulder pain	Groin pain	Peripheral arthralgia	Peripheral arthritis	PET-CT findings (areas with increased FDG uptake)
1	84	M	+	-	-	-	Both shoulders
2	75	F	+	-	+	-	Both shoulders and elbows
3	73	F	+	-	-	-	Both shoulders and elbows
4	72	F	+	-	-	-	None
5	83	F	+	+	-	-	Both shoulders and hips
6	59	F	+	+	-	-	Both shoulders and hips
7	65	F	+	+	+	+	Right shoulder
8	79	M	+	-	+	+	Both shoulders, wrists, hips and knees
9	86	F	+	-	-	-	Both shoulders and hips and posterior part of the L5
10	78	F	+	+	+	+	Both shoulders and knees
11	75	F	+	-	+	-	Both shoulders and hips
12	80	M	+	-	-	-	Both shoulders, elbows and wrists
13	79	F	+	-	-	-	Both shoulders, elbows and wrists

M: Male, F: Female, CRP: C-reactive protein, PET-CT: Positron emission tomography-computed tomography, FDG: F- fluorodeoxyglucose, PMR: Polymyalgia rheumatica

Table 3. Treatment responses and prednisolone doses at the 3rd month of the therapy

	Initial	3rd month	p value
Any symptoms related with PMR, n (%)	13	0	0.0001
CRP, median (IQR), mg/L	26.5 (16-47.25)	5 (2.5-9.5)	0.01
Prednisolone dose*, mean ± SD, mg/day	14.5±1.5	4.5±2.9	0.0001

*Twelve of the 13 patients were treated with prednisolone, SD: Standard deviation, IQR: Interquartile range, CRP: C-reactive protein, PMR: Polymyalgia rheumatica

prednisolone therapy (21). While some studies have suggested an association between PMR and increased malignancy risk, conflicting evidence indicates that no definitive link has been established.

In cases where prednisolone therapy is unsuccessful, clinicians should consider the possibility of concomitant GCA and investigate potential vasculitis. Methotrexate and IL-6 inhibitors may be viable alternatives in cases where prednisolone is inadequate (22-24).

Study Limitations

Our study is limited by its single-center design, the small sample size, and the short follow-up period.

Conclusion

In conclusion, our findings highlight several critical aspects of PMR diagnosis and management. Educating clinicians about the nuanced presentation of PMR and the importance of differential diagnosis can play a crucial role in early detection.

Ethics

Ethics Committee Approval: The study was conducted in full compliance with the principles outlined in the Declaration of Helsinki, and it was conducted after obtaining approval from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 267, date: 13.10.2023).

Informed Consent: Retrospective study.

Footnotes

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

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Determining the Factors Affecting the Satisfaction of Patient in Sedoanalgesia Due to Distal Radius Fracture in Emergency Department

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ABSTRACT

Introduction: Patients with distal radius fractures (DRF) are frequently admitted to the emergency departments (EDs). Reduction with procedural sedation and analgesia (PSA) and followed by plaster/splint are the treatment of choice. We aimed to determine the factors affecting the satisfaction in patients with DRF undergoing PSA.

Methods: This prospective, observational, cross-sectional study included 70 patients with DRF. The socio-demographic features, comorbidities, level of satisfaction with PSA procedure, physical factors of the environment, physician and patient satisfaction were evaluated. PSA satisfaction scores "1, 2 and, 3" were grouped as "dissatisfied group" and "4-5" points as "satisfied group" with the Likert scale. Patient satisfaction was compared between the groups according to the satisfaction levels.

Results: The median satisfaction level was found 4 (interquartile range 4-5). Their satisfaction with the given information about the PSA procedure and the cleanliness of the area where the procedure was performed was higher in the satisfied group than the dissatisfied group (p=0.014 and p=0.007, respectively). Also, as the level of residents of emergency physicians, the satisfaction of the patients increased (p=0.025). There was no significant difference between the groups in terms of age, gender, educational status, comorbidities, fracture type, additional injury, selected sedo-analgesic drugs, Richmond Agitation Sedation Scale and, complications (p>0.05). Satisfaction was high in all physicians.

Conclusion: PSA procedure was satisfactory by a majority and can be performed safely in the ED. The residency period of the physician who performed the PSA, satisfaction with the given information about PSA and the cleanliness of the area were affecting the patient satisfaction.

Keywords: Conscious sedation, radius fracture, patient satisfaction, patient preference, emergency medicine

Introduction

Diagnosis and treatment of fractures are mostly performed in emergency departments (ED). Distal radius fractures account for 20% of all fractures seen in the ED (1). Procedural sedation and analgesia (PSA) is frequently used in the ED to reduce pain and anxiety related to reduction procedures (2).

Although there are numerous studies investigating the success of PSA, those examining patient satisfaction from the patients' perspective are limited (3,4). Patient satisfaction with PSA may vary depending on patient-related or environment-related factors, in addition to the drug choices and administration doses. The aim of our study is to investigate the factors affecting patient satisfaction with PSA during fracture reduction in patients presenting to the ED with a distal radius fracture.

Methods

Our study is an observational, prospective study. Patients over the age of 18 who were admitted to the ED due to distal radius fractures between 1 August 2019 and 1 January 2020 and underwent PSA were included in the study. The study was conducted with the approval of the Ethics Committee of Dokuz Eylül University (approval number: 2019/18-36, date: 17.07.2019). Informed consent was obtained from the patients, and from the physician who performed the interventional procedure, before the study. Patients were excluded from the study for reasons such as refusal to participate, limited communication, unconsciousness,

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additional distracting injuries such as multiple trauma, and the absence of a study team.

Factors that may affect satisfaction with the procedural sedation and analgesia procedure were examined in two groups:

Patient-related factors: Socio-demographic data, comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney failure, psychiatric disease, congestive heart failure, active malignancy, liver disease), fracture type, sedation level achieved in the Richmond Agitation-Sedation Scale (RASS), pain levels before and during the procedure, complications, if any, and interventions made, satisfaction levels about PSA, satisfaction to be informed about the PSA.

Factors related to the physical environment and physician: Characteristics of the area where PSA applied, the patient's perception of the cleanliness of the environment, patients' perception of crowding, duration of physician's experience about the procedure performing reduction and PSA.

Patient satisfaction was evaluated with a 5-point Likert scale when fully awakened after sedation. Patients who scored "1-2-3" on PSA satisfaction were categorized as the "dissatisfied group," and those who scored "4-5" were classified as the "satisfied group."

Fractures were classified as uncomplicated (undisplaced or extra-articular displaced) and complicated (intra-articular displaced or involving fracture of the distal ulna).

All patients were monitored before PSA. There was no intervention in the diagnosis and treatment process (the choice of sedatives and analgesics) of the patients. Sedation levels were evaluated by the study team with the RASS scale. Proper sedation levels for PSA include minimal sedation and moderate sedation [RASS (-3) and RASS (-2)]. Other levels of RASS were considered inappropriate for sedation. In addition, RASS < (-3) values were categorized "excessive sedation" and RASS> (-2) values were "insufficient sedation" in inappropriate sedation group. Respiratory depression (hypoventilation, need for auxiliary respiratory support or airway maneuver), cardiac side effects (arrhythmias, hypo/hypertension), hallucinations, headache, nausea and vomiting, agitation, and epileptic seizure were recorded as complications.

Statistical Analysis

Data were evaluated in SPSS 24.0 package. Descriptive information was summarized by percentage distribution, mean and standard deviation, median minimum-maximum interquartile range (IQR). Variables indicated by counting were compared with the chi-square test and Fisher's exact test, while variables specified by measurement were compared with the Mann-Whitney U test based on their suitability for normal distribution. The Bonferroni test was used for multiple-comparison correction. Independent variables included sedation level, pain scores, crowding perception, cleanliness perception, and physician experience. The statistical significance level was accepted as $p<0.05$.

Results

Seventy of 108 patients with distal radius fractures who received sedation analgesia in the ED were included in the study. Thirty-eight patients were excluded from the study (Figure 1). Fifty-two of the participants (74%) were female, and the median age was 58.5 (IQR: 49.5-67). The median satisfaction level of the patients was found to be 4 (IQR 4-5). Fifty-nine of the patients (84%) were in the satisfied group and 11 of the patients (16%) were in the dissatisfied group (Figure 1). Factors that can affect the satisfaction of the PSA procedure, such as those belonging to the patient, the physical environment, and the physician, are shown in Table 1.

Patient-related factors: Age, gender, education level, comorbidity, type of fracture, and complication rates were similar between the satisfied and dissatisfied patient groups (Table 1).

The median of the RASS scores of the patients during the reduction procedure was: (-2) [IQR: (-3)-(0)].

The median satisfaction score regarding the pre-procedural information about PSA was 5 (IQR 4-5) on a five-point Likert scale. Overall satisfaction with the PSA procedure was higher among those who were satisfied with the information about it ($p=0.014$).

Factors related to the physical environment and physician: No significant difference was found between satisfied and dissatisfied groups regarding the ED area where PSA was applied, and patients' perception of crowding in the ED (Table 2). The median value of the patients' perception of the cleanliness of the environment was 4 (IQR 3-4.3). Satisfied patients had a higher perception of the cleanliness of the environment than the dissatisfied patients.

The median duration of PSA administration was higher in patients satisfied with PSA (12 months) than in patients who were dissatisfied (8 months). There was no difference in patient satisfaction based on the duration of the physician's experience in applying the reduction procedure.

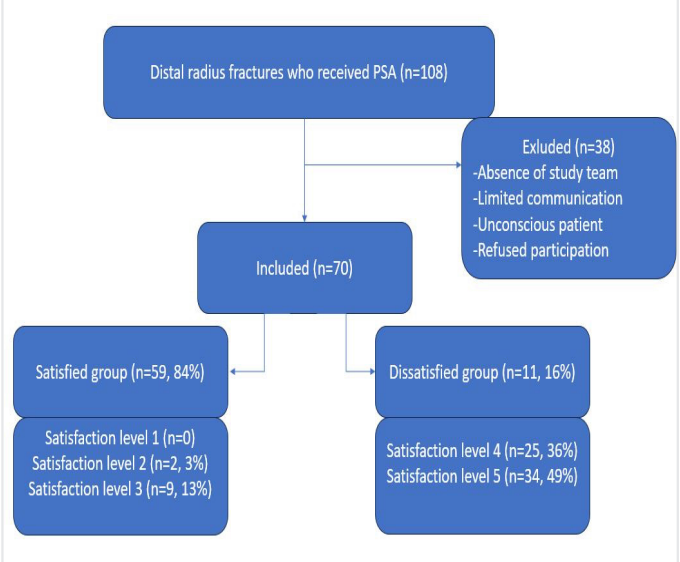

Figure 1. Patient distribution chart
PSA: Procedural sedation and analgesia

Table 1. Patient related factors affecting satifaction

		Patients with dissatisfaction n=11 (%)	Patients with satisfaction n=59 (%)	p
Sex, n (%)	Male	3 (16.7%)	15 (83.3%)	1.000
	Female	8 (15.4%)	44 (84.6%)	
Age (age), median (IQR)		56 (47-67)	59 (50-67)	0.686
Patients education level; n (%)	Graduate	2 (15.4%)	11 (84.6%)	0.922
	Undergraduate	9 (15.8%)	48 (84.2%)	
Comorbidity	At least one	5 (7.1%)	27 (38.5%)	0.985
	None	6 (8.5%)	32 (45.7%)	
Fracture type	Complicated	8 (18.2%)	36 (81.8%)	0.521
	Uncomplicated	3 (11.5%)	23 (88.5%)	
Sedation level	Proper sedation	6 (22.2%)	21 (77.8%)	0.236
	Inappropriate sedation	5 (11.6%)	38 (88.4%)	
Complication	Patients with complication	0 (0%)	6 (100%)	0.542
	Patients without complication	11 (17.2%)	53 (82.8%)	
Pain score before the PSA; median (IQR)		8 (7.25-9.75)	7 (5-9)	0.214
The median of the waiting time before the PSA procedure; minute median (IQR)		30 (15-60)	30 (15-60)	0.915

IQR: Interquartile range, PSA: Procedural sedation and analgesia

Discussion

In our study, it was observed that the majority of patients who underwent PSA in the ED due to distal radius fractures were satisfied with the PSA procedure. In other studies, satisfaction regarding PSA application, in a study using ISAS with a median value of 2.7 (between -3 and +3) a study reporting satisfaction rates of 72-81%, were similarly evaluated to be high (3,5). PSA application in a painful procedure such as bone reduction reduces the pain and anxiety of patients. Therefore, patient satisfaction is also high. Achieving a high satisfaction rate of 84.3% in our study demonstrates effectively that we perform PSA effectively and that the patients are satisfied.

In our study, the application of PSA did not result in any life-threatening complications. The rate of other non-life-threatening complications was 8.6%. In a study conducted in the Netherlands with 1711 patients, the rate of complications associated with PSA application was shown as 10.6 %(5). The PSA complication rates (hypoxia 4.02%, vomiting 1.64%) in the systematic review by Bellolio et al. (6), were similar to those found in our study. The total complication rate in that study was 10.75%. In our study, only four patients developed respiratory depression, which was mitigated with nasal oxygen support, and two patients developed nausea and vomiting. The fact that our complication rate is lower than that reported in other studies shows that we can safely apply PSA in our ED. This may be one of the factors contributing to our high satisfaction rate with PSA. Although the success of the procedure was not evaluated in our study, none of the patients needed to undergo surgery or re-reduction because of unsuccessful reduction. This can be regarded as an indicator of success. With the widespread use of PSA in the ED, satisfaction in painful and difficult procedures is expected to increase. The fact that the majority of our patients (81.4%) stated that they would undergo PSA again if needed supports the confidence and comfort of the patients in PSA application.

Studies in the literature show a relationship between sedation depth and patient satisfaction. In our study, no significant relationship was found between the depth of sedation and patient satisfaction. In an ED study where sedation was followed using the “observers assessment of anaesthesia/Sedation Scale” and the satisfaction was measured with the Iowa satisfaction scale, it was shown that there was a significant relationship between the depth of sedation and patient satisfaction (3). In the referenced study, the number of patients achieving ideal sedation was higher than in our study. In our study, the targeted sedation depth was achieved in 27 patients, less sedation was achieved in 29 patients, and more sedation was achieved in 14 patients. The reason we could not find a relationship between the depth of sedation and satisfaction may be that the effective sedation depth was not sufficiently reached.

Table 2. Factors affecting the satisfaction related to the physical environment and physician				
Factors related to the physical environment				
		Patients with dissatisfaction n=11 (%)	**Patients with satisfaction n=59 (%)**	
ED area where PSA applied	Trauma room	6 (15.8%)	32 (84.2%)	0.542
	Critical care area	2 (8.3%)	22 (91.7%)	
	Observation room	3 (37.5%)	5 (62.5%)	
Patients' perception of crowding in ED	Very calm	0	9	0.205
	Calm	3	20	
	Moderate intensity	4	20	
	Crowded	4	7	
	Very crowded	0	3	
The patient's perception of the cleanliness of the area; median (IQR)		3 (3-3)	4 (3-5)	0.007
Factors related to the physician				
Physicians experience for PSA; month, median (IQR)		8 (2-12)	12 (7-28)	0.025
Physicians experience for reduction; month, median (IQR)		14 (8-18)	15 (10-18)	0.418
IQR: Interquartile range, PSA: Procedural sedation and analgesia, ED: Emergency department				

The median value of the pain level felt by the patients before the procedure is 8 (IQR 6-9), which indicates that patients experience severe pain in distal radius fractures; therefore, the importance of PSA application is emphasized.

In our study, to examine the effect on satisfaction of the properties of the physical area where the PSA procedure is performed, factors such as the specific area in the ED of performance, the density of the environment and the cleanliness of the environment were evaluated. No relationship was found between density and satisfaction, or between the area of the ED where the procedure was performed and satisfaction. On the other hand, the opinions about the cleaning of the area where the PSA was performed were more positive among patients satisfied with the PSA procedure than among those who were not satisfied. We did not find any other data on the cleanliness of the area and on satisfaction in the literature. More studies and evaluations are needed regarding this surprising result.

The median residency (12 months), of the physicians who were satisfied with the PSA procedure was significantly longer than for those whose patients were not satisfied (8 months). The increase in clinical experience is expected to increase the success of the procedure.

Study Limitations

Our study is a single-centered, PSA satisfaction study conducted only in a patient population with distal radius fracture. It cannot be generalized to patients who underwent PSA for other reasons. More comprehensive studies are needed to investigate other parameters that affect PSA satisfaction. In our study, we planned to evaluate the factors affecting physician satisfaction, but we could not make a comparison because all physicians were satisfied with the PSA. The number of patients excluded from the study due to the absence of the study team was high, which we could not have predicted.

Conclusion

In our study, in patients who underwent procedural sedoanalgesia due to distal radius fracture in the ED, we determined that the duration of the residency of the physician who performed the PSA procedure, the physician informing the patient before the PSA, and the cleanliness of the area where the PSA procedure was performed affected patient satisfaction. In our study, patient and physician satisfaction regarding the PSA procedure was also found to be high.

Ethics

Ethics Committee Approval: The study was conducted with the approval of the Ethics Committee of Dokuz Eylül University (approval number: 2019/18-36, date: 17.07.2019).

Informed Consent: Informed consent was obtained from the patients, and from the physician who performed the interventional procedure, before the study.

Footnotes

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

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Investigating the Incidence of Cerebral Microhemorrhage in Active Professional Football Players Through Susceptibility-Weighted Imaging Cerebral Microhemorrhages in Professional Football Players

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ABSTRACT

Introduction: This study assesses the effectiveness of susceptibility weighted imaging (SWI) in detecting microbleeds from repetitive head trauma in active professional football players. The investigation aims to contribute to the ongoing discussion about the long-term neurological effects of professional football and the efficacy of advanced imaging techniques in detecting subtle brain changes.

Methods: We collected data from 60 cases, including 30 professional footballers from the top football league and 30 healthy volunteers. Players' age, average playing time, total number of matches, average matches per player, and total number of traumatic concussions were calculated. SWI was conducted using a 3T magnetic resonance imaging device, and two experienced neuroradiologists independently evaluated the SWI. Group microbleeding rates were compared using the Fisher's exact test.

Results: The average duration of a football career among the participants was 7.14 years, and a total of 5647 matches were held, with an average of 38.4 games per footballer, and 15 traumatic concussions in total. No microhemorrhage was found in SWI of either the footballer or the control group. The evaluations of the two radiologists are in harmony, strengthening the validity of the study's findings.

Conclusion: The study shows no additional micro bleeding in football players compared to the control group, indicating the potential of SWI in detecting traumatic brain injuries. However, this does not necessarily mean that professional football does not cause microbleeds. Further research with larger sample sizes and longitudinal designs is recommended to validate these findings and explore other potential neurological effects of repetitive head trauma in football.

Keywords: Footballers, microbleeding, susceptibility weighted imaging

Introduction

Brain damage as a result of trauma has emerged as one of the most urgent public health concerns in recent years, particularly affecting the young and mobile population. This issue, which can lead to severe disability and even death, is a result of various causes: traffic and work accidents, sports traumas, falling from heights, and physical violence (1). The resulting disorders are categorized into primary and secondary pathologies. Primary pathologies include hemorrhage during trauma, vascular injuries, calvarial fractures, and diffuse axonal injury. Secondary pathologies include biochemical, physiological, and vascular damage caused by disrupting homeostasis within minutes and days after trauma, and by mixing harmful chemicals such as amino acids, neurotransmitters, proinflammatory cytokines, and free radicals into the environment (2).

In American football, rugby, boxing, kickboxing, football, and many other such sports, where close contact is frequent, the risk of concussion due to blows and collisions is prevalent. The increase in the number of athletes participating in these sports has led to a rise in head traumas (3). In football competitions, repetitive head trauma due to collision and excessive exposure to the soccer ball can cause acute and chronic brain damage in the athlete. Acute brain injuries encompass a variety of conditions, including concussion and bleeding, injury to cerebral white matter axons, and even death. Most athletes have reported that memory problems occur in their daily lives long after the match. Studies report that many clinical pictures of behavioral, motor, and cognitive disorders may occur in older adults (4).

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Brain computed tomography (CT) and conventional magnetic resonance imaging (MRI) are the most commonly used radiological methods in the diagnosis of mild brain injury caused by trauma during sports. Normal or nonspecific brain imaging findings are primarily seen in certain radiological methods. Therefore, it is not always possible to diagnose mild traumatic brain injury (TBI) with radiological methods. Although CT and MRI findings were not abnormal, cases with clinical and examination findings consistent with TBI have been published in the literature (5). Studies are being carried out on advanced radiological imaging methods to reveal TBI mechanisms and detect cerebral changes before clinical and examination symptoms appear. As a result, by detecting TBI early, it will be possible to prevent the progression of damage by taking necessary precautions before severe and permanent damage occurs.

MRI is the most commonly used, effective radiological method for the detailed explanation of the anatomy of the brain and the diagnosis of many related pathologies. Thanks to the rapidly developing technological advancements, the modality ranks first in central nervous system imaging with advantages such as multiplanar imaging and being radiation-free. The susceptibility weighted imaging (SWI) technique, developed by Haacke et al. (6) is one of the advanced MRI sequences that display changes in blood oxygen levels, and has emerged with technological developments in recent years. The basis of the SWI technique is the magnetic sensitivity of blood products such as deoxyhemoglobin, intracellular hemoglobin, and hemosiderin, and minerals such as iron and calcium, which results in the acquisition of gradient-weighted images consisting of three-dimensional, high-resolution magnified and phase images and their combinations. This allows the detection of microhemorrhages containing blood products.

Today, with the increase in competitions in football, recognized as the most watched and played sport worldwide, the incidence of TBI is rising due to collisions and repeated heading of the ball. In football players, rapid acceleration, decelerations, contusions, tension, and ruptures in neural and vascular structures may occur due to severe collisions or hard blows to the head by the soccer ball during the match. In TBI, contusion and diffuse axonal injury accompanied by microhemorrhages are observed. As far as we know, an article investigating microhemorrhages in the brain using the SWI method in active football players has yet to be published.

This study marks a significant leap in TBI research. It is a pioneering investigation into the potential of the SWI technique in detecting microhemorrhages resulting from repetitive head trauma in active professional footballers playing in the top football league.

Methods

Informed consent forms were obtained from the participants and the procedure was carried out. The study was approved by the Local Ethics Committee of Selçuk University Faculty of Medicine (approval number: 2020/102, date: 04.03.2020). Our university's Scientific Research Projects unit received financial project support to cover the study's MRI expenses. A total of 60 cases were included in the study, 30 of whom were active professional football players and 30 healthy volunteers of similar age. The age of the players, the average time they played, the total number of matches, the average number of matches per footballer, and the total number of traumatic concussions were recorded. Individuals with neurological or other diseases, including head trauma, epilepsy, metabolic disorders, perinatal asphyxia, active or previous diseases related to the central nervous system, a history of drug and similar substance use, and hypertension were excluded from the study. This exclusion applied to both active professional football players and healthy volunteers. All participants underwent a Mini-Mental Status Examination to assess the possible presence of chronic traumatic encephalopathy, and neurological examinations to rule out diseases such as dementia, depression, tremor, nystagmus, speech disorders, or forgetfulness. Data on the cases included in the study were collected between October 2021 and November 2022.

The MRI examination was conducted meticulously, using an MRI device with a 3T magnetic field strength (Magnetom Aera, Siemens Healthcare, ErlangenGermany) and a head coil. Localizer images were first created in the sagittal plane. For the SWI sequence, the following detailed acquisition parameters were utilized: repetition time, 49 ms, echo time, 40 ms, voxel dimensions, 0.9×0.9×3.0 mm, slice gap overlay, 1, slice thickness, 1.6 mm, base resolution, 320, flip angle, 15°, field of view phase, 75%, and image matrix, 247×320. These optimized parameters were selected to maximize sensitivity for detecting susceptibility effects associated with microhemorrhages while maintaining adequate spatial resolution and signal-to-noise ratio. Since no artifact was detected on SWI, no case was excluded from the study.

All images were evaluated independently by two academic radiologists with 10 and 12 years of neuroradiology experience, regardless of their groups, and the radiologists did not know each other. Corrected phase and magnitude images created using post-imaging software were used for SWI evaluation. The presence of microhemorrhage was investigated using the images. A semi-quantitative analysis method was used to evaluate the sensitivity effects, and was evaluated according to the amount of hypointense foci present in the magnitude images (Figure 1 a-d).

Statistical Analysis

All statistical calculations were performed using IBM SPSS Statistics for Windows version 23, ensuring the objectivity and reliability of the study's conclusions. Microbleeds group rates were compared using the Fisher's exact probability test, and the significance level was set at $p<0.05$.

Results

To investigate the effectiveness of the SWI technique in detecting micro bleeding due to repetitive head trauma in active professional football players, axial plane SWI sequence images of the brains of 60 patients, 30 of whom were from the football player group, and 30 from the healthy control group, were obtained with a 3T MRI device.

SWI of 60 cases were independently evaluated by two academic radiologists with 10 and 12 years of neuroradiology experience, regardless of their groups, unaware of each other's evaluations.

All of the patients participating in the study were male, and the age range was 19-27 years (median 22 years). The average duration of a

football career among the participants was 7.14 years, and a total of 5647 matches were played, with an average of 38.4 games, and 15 traumatic concussions per footballer.

Notably, microhemorrhage was not found in the SWI of either the footballer or the control group. There was no statistically significant difference between the groups. Compliance among radiologists was 100%. The fact that the evaluations of the two radiologists are in harmony further strengthens the validity of the study's findings.

Discussion

The SWI sequence, a novel addition to clinical practice, contrasts using the magnetic susceptibility differences of tissues and differs from T1, T2, T2*, and proton density. This unique approach, sensitive to relaxation changes and phase changes caused by the difference in sensitivity between oxygen and deoxygenated hemoglobin, results in more pronounced signal loss in venous blood. The method creates filtered phase images by applying high- and low-pass filters to the initial raw photos, enhancing the contrast in the original magnified images. These images are duplicated and combined with the original magnified images to create enlarged SWI. This technique has been shown to provide valuable data in the radiological diagnosis of many brain pathologies, making it a compelling area of research for medical professionals. In the past, SWI has been used in the diagnosis of many diseases other than trauma-related brain injury (6). İkizceli and Mutlu Değer (7), a series of SWI studies conducted on 70 patients aged 1-87 years on a 1.5 T MRI device, investigated its sensitivity in detecting lesions such as ischemic cerebral infarction, traumatic and non-traumatic hemorrhage, vascular malformation, intracranial mass, and neurodegenerative disease. As a result, it has been stated that SWI sequences improve visibility and facilitate detection by showing micro- and macrohemorrhages, venous malformations, and mineral accumulation better than conventional MRI sequences (8). In a study of 180 patients with traumatic-non-traumatic hemorrhage, masses, foci of microbleeding, vascular malformation, ischemic cerebral infarction, cerebral mineral accumulation due to systemic or neurodegenerative disease, multiple sclerosis, and non-specific findings, without loss of detail in anatomical formations, the SWI sequence detected slow-flow vascular lesions, large and small hemorrhage foci, mineral accumulation in cerebral strokes, the internal structure of cerebral masses, and hemorrhagic. It has been noted that a new MRI sequence is highly effective and sensitive in detecting transformation (8).

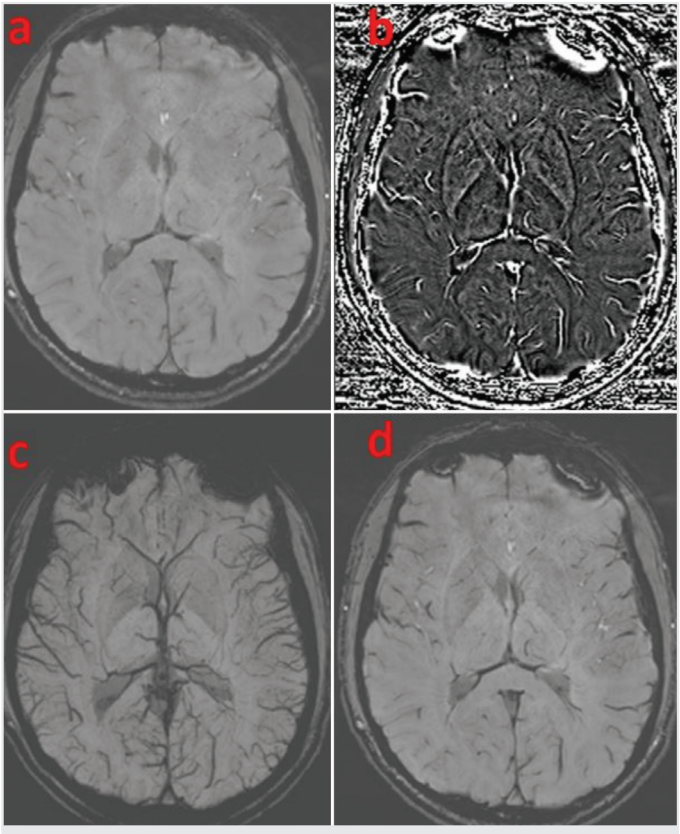

Figure 1. SWI a) magnitude image b) filtered phase image c) minIP image d) processed SWI

SWI: Susceptibility weighted imaging, minIP: Minimum intensity projection

In recent years, studies on sports-related TBI were primarily conducted in boxers. One of these studies was performed with CT and evaluated 388 active professional boxers; 93% had normal brain CT findings, and 6% had borderline atrophy (9). In another study conducted with MRI and attended by 12 active and 40 retired boxers, mild cerebral atrophy was described in 8 cases, and mammillary bodies and optic chiasm were described as small in 30 cases (10). In a 1992 study using MRI, no brain abnormalities or brain microhemorrhages were detected in the systematic study of 13 amateur boxers, despite the technical limitations of the early days of MRI. This study obtained images using a 10 mm thick 0.5 T MRI device (11). Unlike these studies, the introduction of SWI, a more sensitive and up-to-date technique, was a significant advancement. This study used this method for the first time to detect microbleeding in active professional football players, marking a crucial step forward in the field. In addition, factors affecting the severity and recurrence of trauma, such as match severity, previous severe trauma, and encephalopathy, were also taken into account.

To elucidate the pathologies in the boxing population using up-to-date MRI techniques, studies have been initiated to detect recent and minor bleeding. Although the survey evaluated images including transverse dual spin echo, rapid gradient echo acquisition prepared by 3D sagittal magnetization, and axial flight-time MR angiography sequences in coronal T2* and 3T devices, as well as fight and knockout numbers, weight distribution, and duration of boxing, and found a statistically higher frequency of cerebral microbleeding than in non-boxers, this difference was not statistically significant (12). The study investigated the differences between conventional MRI, T2 FSE, T2* GE, and 1.5T MRI devices (including SWI). Microbleeding was detected in 2 of 21 boxers. Although more micro-bleeding was detected in amateur boxers than in the control group, the difference was not considered statistically significant (13). One of the technical differences in this study is using a 3T MRI device. This has led to greater sensitivity in detecting microbleeding. The fact that experienced neuroradiologists perform the evaluation without being aware of each other, and that the results are compatible, are among the factors that increase the reliability of the SWI sequence. In addition, the absence of micro bleeding in the group of football players in our study can be explained by the football players

being younger, and the number of severe trauma and encephalopathy was low. In addition, the fact that the traumas experienced during football were not directed to the head, as is common in boxing, may have affected the results.

In the SWI study conducted to determine the changes due to concussion in a total of 45 male and female ice hockey players in Canada, at the beginning and end of the season, it was reported that the SWI sequence helped determine the severity of cerebral microhemorrhage foci and follow-up. In addition, it was found that the cerebral microhemorrhage burden of boys was higher than that of girls, especially in the first two weeks following concussion (14). In the case report of IM Asif et al. (2), the presence of cerebral microhemorrhages was demonstrated by SWI sequence in a university football player who suffered a concussion, and the risks and clinical significance associated with cerebral microhemorrhages in the young athletic population were not determined. It has been emphasized that the findings of current neuroradiological imaging in the management of sports-related concussions have potential benefits for the return to play. However, the importance of further research is urgent and cannot be underestimated. There are not enough SWI studies in the literature on TBI resulting from head traumas seen in football. In a comprehensive randomized prospective study involving four European countries, which examined head and neck injuries in children aged 7-12 years, it was reported that 39 of the total 791 injuries were head injuries and one was a neck injury. Head injuries were seen in the form of concussion, contusion, laceration, or abrasion, nasal fracture, and dental injury (15). Radiological imaging findings were not included because no imaging modality was used in this study. In the future, studies with SWI can show microhemorrhages in the brain that may occur in child athletes, leading to the implementation the necessary treatments in a timely manner. Our study is critical in terms of providing insight into this subject.

Study Limitations

Due to its unique focus on active professional football players, our study faced several challenges. First, the limited number of players in the top football league made it challenging to conduct MRIs. Second, we could only record official matches, despite the players' history of training and unofficial matches. Lastly, while SWI is a sensitive imaging technique, chronic bleeding may not always appear in the SWI sequence due to resorption over time, potentially leading to missed data. Another limitation of our study is the inability to evaluate the relationship between factors such as players' field positions, heading dominance, height characteristics, and SWI findings. These factors may be determinative, particularly in terms of the frequency and severity of head trauma, and should be considered in future studies.

Conclusion

SWI, a highly reliable method for detecting cerebral microhemorrhages, which is a severe form of TBI in active professional football players, has the potential to bring about substantial advances in the field. The study did not find increased microbleeding in football players compared to the control group, and this is a promising finding. To gain a deeper understanding of the efficacy of SWI, it is essential to perform imaging in large study groups of professional football players who have a high number of recurrent histories of severe trauma and are at risk of developing chronic traumatic encephalopathy. This could lead to substantial advances in preventing and treating TBIs in football, the most popular sport today, providing hope and progress in sports medicine.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Selçuk University Faculty of Medicine (approval number: 2020/102, date: 04.03.2020).

Informed Consent: Informed consent forms were obtained from the participants and the procedure was carried out.

Footnotes

Authorship Contributions: Concept - M.Ö., K.D.; Design - M.Ö., A.B., K.D.; Data Collection or Processing - M.Ö., A.B., A. Bayr., K.D., H.C.; Analysis or Interpretation - M.Ö., A. Bayr., A.B., H.C.; Writing - M.Ö., A. Bayr.

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Predictive Value of Onodera's Prognostic Nutritional Index for Short-Term Mortality in Subjects with Acute Pulmonary Embolism

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ABSTRACT

Introduction: The Pulmonary Embolism Severity Index (PESI) is a widely used tool for assessing prognosis and predicting 30-day mortality in acute pulmonary embolism (APE) patients. Onodera's Prognostic Nutrition Index (OPNI) is a simple tool that provides information on the nutritional status and prognosis of subjects, especially in gastrointestinal system malignancies. This academic work aims to evaluate the relationship between the OPNI score, which is a simple risk stratification tool, and the PESI score, short-term mortality (STM) in subjects diagnosed with pulmonary embolism (PE).

Methods: A total of 176 PE subjects were included in this retrospective academic work. The PESI scores and OPNI scores of all subjects were calculated using the formula serum albumin (g/L) + 0.005 × total lymphocyte count (cells/mm^3). The primary outcome of the academic work was accepted as the in-hospital mortality along with STM rate within 30 days from the time of diagnosis.

Results: The mean age of all subjects, PESI score, and OPNI score were 62.93±16.57, 98.83±39.35, and 42.86±8.06, respectively. There was a considerable inverse relationship between PESI score and OPNI (r=-0.401, p<0.001). In multivariate analysis, OPNI value [odds ratio (OR): 0.89, 95% confidence interval (CI): 0.83-0.96; p=0.002), cancer history (OR: 3.62, 95% CI: 1.30-10.10; p=0.014), oxygen saturation (OR: 0.86, 95% CI: 0.80-0.93; p<0.001) and male sex (OR: 2.73, 95% CI: 1.02-7.34; p=0.047) were found to be independent predictors of STM. The optimal OPNI cut-off value for predicting STM, based receiver operating characteristic curve analysis was ≤39.17, yielding a sensitivity of 75.5% and specificity of 67.6%.

Conclusion: OPNI appears to be a promising, easily applicable, operator-independent and cost-effective parameter for predicting STM in subjects with APE.

Keywords: Pulmonary embolism, Pulmonary Embolism Severity Index, Onodera's Prognostic Nutrition Index, short-term mortality

Introduction

Pulmonary embolism (PE) is the third most common cause of mortality among cardiovascular diseases; symptoms range from dyspnea to life-threatening hemodynamic instability due to occlusion of one or more pulmonary arteries. Early diagnosis of high-risk subjects has been known to reduce the risk of death and strongly effects the selection of treatment modalitysuch as anticoagulation therapy, thrombolysis or surgical intervention (1). The risk of short-term mortality (STM) of PE by utilizing clinical parameters and/or biomarkers such as troponin and B-type natriuretic peptide, individually or in combination at the time of admission has been investigated by several scoring systems. The most widely used Pulmonary Embolism Severity Index (PESI) assesses the prognosis of PE subjects and provides a well-documented risk stratification for 30-day mortality (2).

Onodera's Prognostic Nutrition Index (OPNI) has been defined as a simple tool that provides information about the patient's nutritional status and prognosis in subjects with chronic diseases, particularly in gastrointestinal system malignancies (3). Albumin, a negative acute phase reactant, and the lymphocyte count indicating immune function are included in the formula, and OPNI can be simply calculated as: serum albumin (g/L) + 0.005 × total lymphocyte count (cells/mm^3). A lower OPNI score has generally been associated with worse nutritional status, chronic inflammation and poor prognosis (4-6).

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The aim of this academic work was to evaluate the association between the OPNI score, which is a simple risk stratifying tool compared to PESI, and STM in acute PE subjects.

Methods

A total of 221 consecutive cases with acute pulmonary embolism (APE) admitted to both clinics between November 2018 and the current year were enrolled. After excluding 45 subjects with incomplete clinical or laboratory data and missing 30-day follow-up finally 176 APE subjects were included in this retrospective acedemic work. Demographic characteristics, clinical, laboratory, electrocardiographic, and echocardiographic findings were collected from the electronic databases of the hospitals. OPNI score of all subjects was calculated using the formula serum albumin (g/L) + 0.005 × total lymphocyte count (cells/mm^3) based on laboratory values at first admission. All subjects were treated for PE in accordance with current guidelines. Local Ethics Committee approval (approval number: 73, date: 06.09.2024) was obtained for the study in University of Health Sciences Türkiye, İstanbul Training and Research Hospital, and the academic work was conducted in accordance with the Declaration of Helsinki Principles.

Electrocardiographic records of all subjects at the time of hospitalization or pre-assessment were reviewed, and the presence of sinus rhythm or atrial fibrillation, sinus tachycardia and negative T waves in leads V1-V4 were recorded. Echocardiographic recordings were also collected using a Philips EPIQ 7 device (Philips Healthcare, USA) with a 2.5 MHz probe. In addition to left ventricular (LV) ejection fraction measured with the Modified Simpson method, LV end-diastolic diameter, right ventricular diameter, Tricuspid Annular Plane Systolic Excursion value, and the presence of mid/advanced tricuspid valve regurgitation, were noted (7). Pulmonary artery systolic pressure was determined by adding the value obtained using the Simplified Bernoulli Equation to the right atrial pressure calculated according to inferior vena cava diameter and respiratory variation (8). APE was diagnosed by an experienced radiologist using multi-slice spiral computed tomography pulmonary angiogram (CTPA) (Toshiba Medical Systems Corporation, Japan) according to the presence of complete or partial luminal filling defects in the pulmonary artery branches. Laboratory parameters were obtained from samples taken at the time of admission to the emergency department. Hematological parameters were measured using Sysmex hematology analyzers (Sysmex Corporation, Japan) as part of an automated complete blood count. Plasma D-dimer levels were measured via an immune-turbidimetric assay, while biochemical parameters, especially albumin levels, were evaluated by Beckman Coulter kits and calibrators. Troponin I levels were quantified through a chemiluminescence immunoassay method (Access 2 Immunoassay System; Beckman Coulter, Inc.).

Subjects presenting with hemodynamic instability such as shock, hypotension, or cardiac arrest were classified as high-risk irrespective of their PESI score. In contrast, subjects who were not deemed high risk were categorized as intermediate or low risk based on their PESI score and evidence of right ventricular dysfunction on imaging or laboratory findings (1,2). In-hospital mortality and STM within 30 days from the time of diagnosis were the primary outcomes of this study. Death due to any cause within the first 30 days was considered STM. All short-term clinical events were obtained from the hospital information system or national healthcare system, and subjects were divided into two groups according to the occurrence of STM.

Statistical Analysis

While categorical variables were given as numbers and percentages, the normality of continuous variables was evaluated with the Shapiro-Wilk test, and continuous variables were given as mean ± standard deviation. When numerical variables met the normal distribution condition, the Student's t-test was used; when the normal distribution condition was not met, the Mann-Whitney U test was used; and categorical variables were compared with the chi-square test or Fisher's exact test. Correlation analyses were calculated using Pearson or Spearman correlation tests. Univariate analyses and multivariate logistic regression analysis were used to identify independent predictors for STM, and hazard ratios (HR) and 95% confidence intervals were calculated. Receiver operating characteristic (ROC) curve analysis was performed to determine the discriminatory ability of OPNI for STM based on specificity and sensitivity. Additionally, the optimal cut-off value of OPNI was calculated from the point of maximal sensitivity and specificity using Youden's index (sensitivity + specificity - 1) (9). The effect size (Cohen's d: 0.71) and power value (1-β: 0.95) of OPNI for STM were calculated using G*Power software (version 3.1.9.2). Analyses were performed using SPSS version 23.0 (IBM, Chicago, Illinois) with a $p<0.05$ indicating statistical significance.

Results

A total of 176 subjects (n=97, 55.1% female) were evaluated. The mean age and PESI score of all subjects were 62.93±16.57 and 98.83±39.35, respectively. The proportion of subjects with PESI class IV-V was 36.4%. Demographic characteristics, admission clinical parameters, and electrocardiogram characteristics of all subjects were presented in Table 1. While male sex, congestive heart failure, history of cancer, and PESI class-V were substantially higher in the STM group, the rate of PESI class I-II was lower. There was no significant difference in the admission electrocardiographic characteristics. Laboratory and echocardiographic parameters at admission are presented in Table 2. The mean OPNI score of all subjects was 42.86±8.06. Lymphocyte count, albumin values, and OPNI score were statistically significantly lower in the STM group. No significant difference was found between the groups among echocardiographic parameters except LV ejection fraction. The correlation analysis between admission PESI score and admission characteristics, echocardiographic parameters and OPNI is given in Table 3. A statistically negative relationship was detected between PESI score and OPNI ($r=-0.401$, $p<0.001$). In multivariate analysis, the independent predictors of STM were history of cancer (HR: 2.25, $p=0.034$), oxygen saturation (HR: 0.92, $p=0.001$), and OPNI value (HR: 0.92, $p=0.005$), and these variables are shown in Table 4. The ROC analysis is given in Figure 1. The ROC curve analysis determined that OPNI ≤39.3 was the optimal cut-off value for discriminating between high-risk and low-risk subjects for STM, with a sensitivity of 70% and a specificity of 73%, respectively.

The Kaplan-Meier curves in Figure 2 represent the STM in subjects divided into low and high-risk groups, according to the determined cut-off value of OPNI.

Discussion

The present acedemic work aimed to investigate the prognostic value of OPNI, a simple and easily calculable index based on serum albumin levels and lymphocyte count, instead of PESI which is a more complex assessment score to demonstrate 30-day mortality in subjects with APE. Our results showed that subjects with lower OPNI scores had significantly higher STM, suggesting that it can be used as a prognostic tool in the clinical management of APE.

In recent years, numerous tools have been investigated to assess the short-term risk of death in APE subjects, including various risk scores, imaging modalities, and biomarkers, the most commonly used of which is the PESI. The role of biomarkers such as troponins, brain natriuretic peptides, and D-dimer is well established in determining right ventricular dysfunction, patient prognosis, and hemodynamic impairment in APE subjects. These biomarkers reflect myocardial damage, right ventricle (RV) dysfunction and hemodynamic instability, all of which are important factors in determining patient prognosis (10). In addition to biomarkers, imaging modalities such as echocardiography and CTPA, which are important in assessing RV function and pulmonary artery pressure, provide insights about mortality. Previous studies have

Table 1. Baseline demographic characteristics findings of all patients

	All patients, (n=176)	Mortality, (n=37)	Survivor, (n=139)	p
Age, years	62.93±16.57	66.70±15.87	61.93±16.66	0.148
Female gender, n (%)	97 (55.1)	14 (37.8)	83 (59.7)	0.017
Hypertension, n (%)	71 (40.3)	11 (29.7)	60 (43.2)	0.139
Diabetes mellitus, n (%)	39 (22.2)	10 (27.0)	29 (20.9)	0.422
Congestive heart failure, n (%)	21 (11.9)	9 (24.3)	12 (8.6)	0.019
Cerebrovascular disease, n (%)	11 (6.3)	5 (13.5)	6 (4.3)	0.055
COPD, n (%)	19 (10.8)	6 (16.2)	13 (9.4)	0.240
Acute kidney failure, n (%)	3 (1.7)	1 (2.7)	2 (1.4)	0.510
Cancer, n (%)	38 (21.6)	16 (43.2)	22 (15.8)	<0.001
On admission				
PESI score	98.83±39.35	130.75±42.08	90.21±33.89	<0.001
PESI class, n (%)				
I	36 (20.5)	2 (5.4)	34 (24.5)	<0.001
II	36 (20.5)	2 (5.4)	34 (24.5)	
III	40 (22.7)	9 (24.3)	31 (22.3)	
IV	31 (17.6)	7 (18.9)	24 (17.3)	
V	33 (18.8)	17 (45.9)	16 (11.5)	
Systolic blood pressure, mmHg	127.97±27.04	119.09±29.60	130.23±25.98	0.002
Diastolic blood pressure, mmHg	73.47±14.02	72.57±17.29	73.69±13.12	0.234
Heart rate, beats per minute	97.38±18.92	102.89±19.98	95.99±18.46	0.083
SaO_2, (%)	90.69±6.01	87.41±7.42	91.57±5.26	0.001
Admission electrocardiogram				
Normal electrocardiogram, n (%)	90 (51.1)	16 (43.2)	74 (53.2)	0.748
Sinus tachycardia, n (%)	56 (31.8)	14 (37.8)	42 (30.2)	
Atrial fibrillation, n (%)	22 (12.5)	5 (13.5)	17 (12.2)	
Negative T wave in V1-V4, n (%)	8 (4.5)	2 (5.4)	6 (4.3)	
Admission echocardiography				
Left ventricular ejection fraction, (%)	55.42±9.79	51.14±11.57	56.72±8.84	0.003
LV end-diastolic diameter, mm	47.85±5.02	49.24±4.96	47.41±4.99	0.130
Left atrial diameter, mm	38.51±7.05	38.63±6.85	38.47±7.17	0.994
Right ventricular diameter, mm	28.60±6.42	28.83±5.98	28.54±6.58	0.764
TAPSE, mm	2.20±0.47	2.14±0.40	2.21±0.49	0.495
sPAP, mmHg	37.30±13.20	39.74±11.14	36.71±13.65	0.463
Moderate/severe TR, n %	44 (25.0)	25 (67.6)	12 (32.4)	0.240

Continuous variables are presented as mean ± standard deviation; nominal variables are presented as frequency (%). COPD: Chronic obstructive pulmonary disease, PESI: Pulmonary embolism severity index, SaO_2: Arterial oxygen saturation, TAPSE: Tricuspid Annular Plane Systolic Excursion, sPAP: Systolic pulmonary artery pressure, TR: Tricuspid regurgitation

Table 2. Laboratory and echocardiographic findings of all patients

	All patients, (n=176)	Mortality, (n=37)	Survivor, (n=139)	p
Laboratory variables				
D-dimer, ng/mL	5.53±5.54	5.36±5.32	5.58±5.65	0.907
Troponin I, pg/mL	65.55±120.54	80.28±133.34	61.69±117.34	0.759
Creatinine, mg/dL	0.90±0.48	0.91±0.46	0.89±0.49	0.820
Glucose, mg/dL	146.77±73.65	154.14±60.16	144.77±76.99	0.495
ALT, U/L	29.51±39.67	44.89±71.14	25.41±24.40	0.008
AST, U/L	35.24±43.84	58.51±85.92	29.00±17.77	<0.001
White blood cell, cells/µL	10.66±4.69	11.37±5.31	10.47±4.52	0.305
Hemoglobin, g/dL	11.89±2.13	11.40±1.73	12.02±2.21	0.119
Platelets, cells/µL	250.59±106.82	222.86±83.08	257.96±111.39	0.076
Lymphocyte	1.62±0.86	1.39±0.86	1.68±0.85	0.027
Albumin	34.76±6.26	29.95±5.91	36.04±5.72	<0.001
OPNI score	42.86±8.06	36.92±7.05	44.44±7.58	<0.001
Admission echocardiography				
Left ventricular ejection fraction, (%)	55.42±9.79	51.14±11.57	56.72±8.84	0.003
LV end-diastolic diameter, mm	47.85±5.02	49.24±4.96	47.41±4.99	0.130
Left atrial diameter, mm	38.51±7.05	38.63±6.85	38.47±7.17	0.994
Right ventricular diameter, mm	28.60±6.42	28.83±5.98	28.54±6.58	0.764
TAPSE, mm	2.20±0.47	2.14±0.40	2.21±0.49	0.495
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Moderate/severe TR, n %	44 (25.0)	25 (67.6)	12 (32.4)	0.240

Continuous variables are presented as mean ± standard deviation, nominal variables presented as frequency (%). ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, OPNI: Onodera's Prognostic Nutritional Index, sPAP: Systolic pulmonary artery pressure, TAPSE: Tricuspid Annular Plane Systolic Excursion, TR: Tricuspid regurgitation

Table 3. Correlation of PESI score with baseline characteristics, echocardiographic findings, OPNI

Correlation between	R-value	p
Age	0.597**	<0.001
Systolic blood pressure	-0.222**	0.004
Diastolic blood pressure	-0.152*	0.047
Heart rate	0.283**	<0.001
RV TAPSE	-0.279	0.129
LVEF	-0.420**	<0.001
PASP	0.312**	0.002
Troponin I	0.182*	0.035
OPNI	-0.401**	<0.001

LVEF: Left ventricular ejection fraction, OPNI: Onodera's Prognostic Nutritional Index, PASP: Pulmonary artery systolic pressure, PESI: Pulmonary Embolism Severity Index, RV: Right ventricle, TAPSE: Tricuspid Annular Plane Systolic Excursion, *p<0.05, **p<0.01

shown that subjects with RV enlargement and dysfunction, as well as high pulmonary artery pressure, have a poor prognosis (11).

Instead of body mass index or serum albumin levels, which indicate nutritional status, physical, and immunologic competence, various scoring systems such as CONUT and OPNI have been developed (12,13). The fact that these scoring systems can be calculated simply and cost-effectively seems to be an advantage. The finding in this analysis suggests that lower OPNI values, which were significantly related to STM, indicate that nutritional status and immune function may play an important role in APE patients' outcomes.

Studies have shown that low albumin levels, usually an indicator of malnutrition or systemic inflammation, and decreased lymphocyte counts, an indicator of immunosuppression, affect mortality or poor survival in some diseases (14,15). A review of 29 studies showed that pre-treatment albumin levels below 35 g/L were associated with poor outcomes in almost all cancer types. In our study, the albumin level was 36.04±5.72 in the surviving group and 29.95±5.91 in the group with STM, values which are similar to those reported in the literature (16). It has been shown that decreased lymphocyte counts, which are an indicator of immunosuppression, are associated with mortality in subjects with pneumonia; with mortality at 13.6% between lymphocyte values 0-1 and 9.2% between lymphocyte values 1-2, and mortality decreased further with an increase in lymphocyte values (17). In our study, similar to the literature, lymphocyte values were found to be 1.39±0.86 lower in the STM group. In 220 small cell lung cancer subjects, an OPNI score <40 derived from pre-treatment albumin and lymphocyte values has been shown to be associated with low tolerance to chemotherapy and poor prognosis (4). From another perspective, the fact that it emerged as an independent predictor of STM in regression analysis and that a lower OPNI score (≤39.17) was related to an increased probability of STM supports the link between OPNI and poor outcome in APE patients in our study.

History of cancer and low oxygen saturation were found to be other important predictors of STM. In a cross-sectional study with 5,152 participants to determine whether low oxygen saturation was associated with increased mortality in the general adult population, SpO_2

Table 4. The independent effects of some possible predictors in relation to short-term mortality according to univariate/multivariate analysis

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age, years	1.02 (0.99-1.04)	0.167		
Female, gender	2.02 (1.04-3.92)	0.038	1.85 (0.88-3.88)	0.102
CHF	2.37 (1.12-5.03)	0.024	1.83 (0.76-4.42)	0.181
Malignite	2.77 (1.44-5.30)	0.002	2.25 (1.06-4.75)	0.034
SaO_2	0.93 (0.89-0.97)	0.001	0.92 (0.87-0.96)	0.001
Systolic blood pressure	0.99 (0.97-1.00)	0.137		
Heart rate	1.01 (1.99-1.03)	0.085		
Troponin	1.00 (0.99-1.00)	0.471		
LVEF	0.97 (0.94-0.99)	0.011	0.99 (0.96-1.02)	0.473
PABS	1.01 (0.98-1.05)	0.418		
OPNI	0.91 (0.87-0.95)	<0.001	0.93 (0.89-0.98)	0.005

HR: Hazard ratios, CI: Confidence interval, CHF: Congestive heart failure, SaO_2: Arterial oxygen saturation, LVEF: Left ventricular ejection fraction, PASP: Pulmonary artery systolic pressure, OPNI: Onodera's Prognostic Nutritional Index

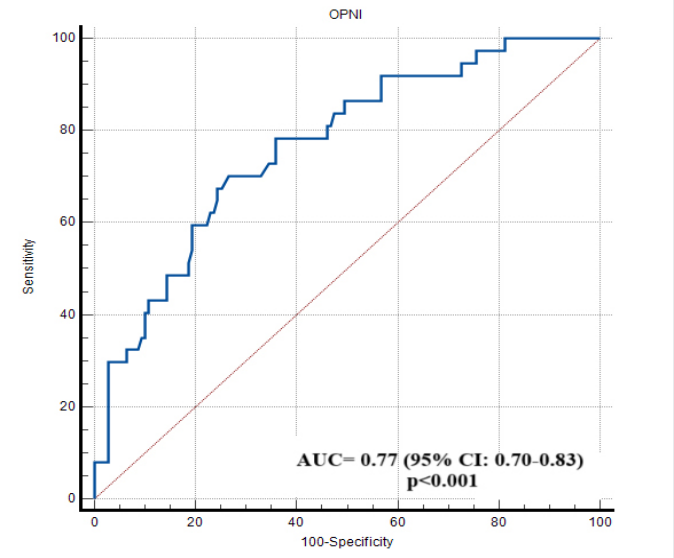

Figure 1. On receiver operating characteristic (ROC) analysis, area under the ROC curve (AUC) value of OPNI for short-term mortality was 0.77 (95% CI: 0.70-0.83, p<0.001)
CI: Confidence interval, OPNI: Onodera's Prognostic Nutrition Index

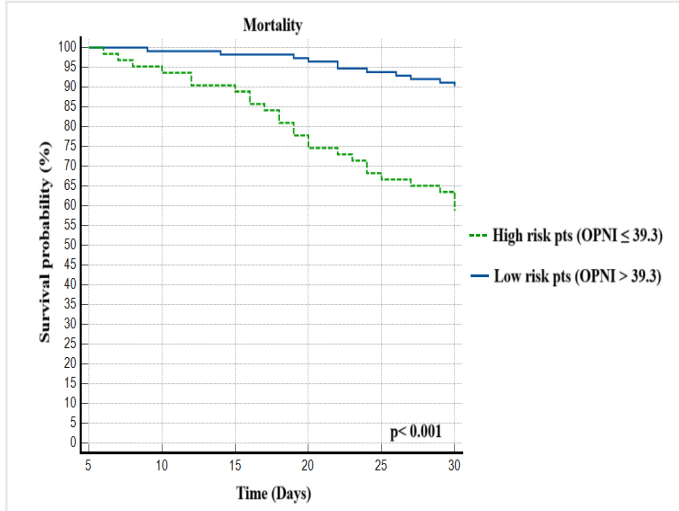

Figure 2. Kaplan-Meier plots show survival curves for low (blue line) and high (green line) risk patients based on the established OPNI cut-off value
OPNI: Onodera's Prognostic Nutrition Index

≤92% increased mortality by a factor of 1.73 times in a multivariable regression model for all-cause mortality. It has also been shown that in various diseases, which cause low oxygen levels, with or without lung pathology, increase mortality by worsening the burden on the RV and overall hemodynamic stability (18). In our study, oxygen saturation, a critical marker of lung function that can be evaluated quickly and easily, was also shown to be an important determinant of mortality. It is well known that a history of cancer is both a risk factor for PE and a predictor of mortality (19,20).

In a single-center registry study of 896 consecutive PE subjects followed for up to 14 years, Eckelt et al. (21) showed that a history of cancer was the strongest predictor of mortality compared to the general population, which is in line with our results.

Study Limitations

Despite the promising results, our acedemic work has several limitations. First, the retrospective design, relatively small sample size, and small number of participating centers limit the study's generalizability. It needs to be validated with future appropriately sized, randomized, prospective studies. Second, while our study focused on STM, investigating the effect of OPNI on long-term mortality, may enhance the study's outcomes. Finally, OPNI was evaluated as a single parameter rather than an index; however, it can be used as an index with the inclusion of additional parameters such as echocardiographic findings and more detailed clinical characteristics.

Conclusion

OPNI appears to be a promising, easily applicable, practitioner-independent and cost-effective parameter for predicting STM in subjects

with APE. Based on the findings from our study, the OPNI may be an effective complement or alternative to the PESI, especially in settings with limited access to comprehensive clinical data and when patient communication is difficult.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (approval number: 73, date: 06.09.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Concept - M.K., Ş.T., G.Y., S.T., F.Ö., T.K., A.Ö.; Design - M.K., Ş.T., G.Y., S.T., F.Ö., T.K., A.Ö.; Data Collection or Processing - M.K., Ş.T., G.Y., S.T., F.Ö., T.K., A.Ö.; Analysis or Interpretation - T.K., A.Ö.; Literature Search - M.K.; Writing - M.K., T.K., A.Ö.

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Uric Acid Levels in Individuals with Obesity: Association with Cardiovascular Disease Risk

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ABSTRACT

Introduction: Obesity is one of the main health problems of modern societies. It is known to be one of the leading causes of cardiovascular diseases, as well as diseases such as hypertension and diabetes. Here, we aimed to investigate whether the Framingham Risk Scoring (FRS) system and uric acid (UA) levels can be used as cardiovascular risk markers in individuals with obesity.

Methods: The study included 203 patients with body mass index (BMI) ≥30 kg/m^2, between the ages of 18-65 years, followed up in the obesity outpatient clinic in the last 5 years. Age, gender, chronic diseases, smoking status, systolic/diastolic blood pressure, height, weight, BMI, waist circumference, hip circumference, waist/hip ratio prescribed medications, fasting blood glucose, insulin level, hemoglobin A1c (HbA1c), total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, and serum UA values were recorded from patient files. The FRS was calculated. Results were evaluated using SPSS.

Results: When the two groups were compared based on the median serum UA value of 5.3 mg/dL, those with serum UA <5.3 mg/dL were defined as group 1, and those with serum UA ≥5.3 mg/dL were defined as group 2. When the 2 groups were compared, there was no significant difference between the FRSs. The FRS was correlated with age, height, waist circumference, waist/hip ratio, systolic and diastolic blood pressure, fasting blood glucose, total cholesterol, LDL cholesterol, triglyceride, and insulin levels, and HbA1c level. Serum UA level was correlated with weight, waist circumference, hip circumference, BMI, systolic and diastolic pressure, triglycerides, and insulin levels. UA level was found to be associated with the FRS.

Conclusion: UA levels, in addition to traditional cardiovascular risk markers and scoring systems, can be used to predict cardiovascular risk in individuals with obesity.

Keywords: Obesity, Framingham Risk Score, serum uric acid

Introduction

Heart-related illnesses rank among the top reasons for death globally. It is thought that approximately one-third of the deaths in the world are due to cardiovascular disease (CVD) (1). Obesity is one of the main health problems in modern societies and reaches epidemic rates in many developed countries. It is known to be one of the leading causes of CVD along with many other diseases such as hypertension and diabetes (2). Given the widespread occurrence of CVD, assessing the likelihood of cardiovascular events is crucial for reducing associated deaths and illnesses (3). Framingham Risk Score (FRS) was introduced by Wilson et al. (4) in 1998 and is a risk calculator that determines the 10-year risk of developing CVD. With FRS assessment, 10-year cardiovascular risk can be estimated with 75% accuracy (5).

In humans, uric acid (UA) represents the final product of purine metabolism, whether from dietary sources or endogenous production. The liver synthesizes this compound, which is subsequently eliminated by the kidneys (6). Increased UA levels have been found to be closely associated with diabetes mellitus (DM) (7), metabolic syndrome (8), hypertension (9), and abdominal obesity (10). While the impact of UA levels on CVD development remains debatable, its involvement in inflammatory processes is well-established (11).

Our research sought to examine the correlation between serum UA concentrations and the 10-year CVD risk as calculated by the FRS system in individuals with obesity. Additionally, we aimed to evaluate the potential of UA levels as an indicator of cardiovascular risk in this population.

Methods

The research adhered to the principles outlined in the 1964 Helsinki Declaration. All participants provided their informed consent. The study received ethical clearance from University of Health Sciences Türkiye,

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İstanbul Training and Research Hospital (approval number: 1898, date: 28.06.2019).

Patient Population

We conducted a retrospective analysis involving 203 patients who met the inclusion criteria and had been monitored at the obesity outpatient clinic over the past 5 years. The research encompassed individuals aged 18-65, with a body mass index (BMI) ≥30 kg/m^2, who had established records at the obesity outpatient clinic within the last 5 years, possessed complete documentation, had all necessary laboratory values, and attended regular follow-up appointments. We excluded participants diagnosed with chronic renal failure, malignancy, or gout, as well as those taking medications that affect UA metabolism.

We performed a retrospective examination of the follow-up forms for patients monitored at the obesity outpatient clinic. We documented various parameters including age, gender, chronic diseases, smoking status, systolic/diastolic blood pressure, height, weight, BMI, waist circumference, hip circumference, waist/hip ratio, and prescribed medications.

Laboratory Analysis and Framingham Risk Score Calculation

The laboratory data of the patients were obtained from the outpatient clinic records of our hospital's electronic records system. Fasting blood glucose, insulin, hemoglobin A1c (HbA1c), total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and serum UA values were recorded based on the dates of the first presentation to the obesity outpatient clinic. The FRS system was employed to assess the CVD risks of the patients. The calculation of the total risk score incorporated several factors, including gender, age, smoking status, total cholesterol levels, HDL-C values, systolic blood pressure, other risk factors, and the use of anti-hypertensive medication. For each gender, scores were assigned to these factors based on the Framingham risk table. The overall risk scores were then determined by adding up the individual scores for each risk factor. According to the FRS, those with a score lower than 10 were considered to have a low 10-year cardiovascular risk, those with a score between 10 and 19 were considered to have an intermediate risk, and those with a score greater than 20 were considered to have a high risk.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov-Smirnov test. Independent samples t-tests, Kruskal-Wallis tests, and Mann-Whitney U tests were used to analyze quantitative independent data. The chi-square test was used to analyze qualitative independent data. The effects were investigated by univariate and multivariate logistic regression. The SPSS 26.0 was used for the analysis. A $p<0.05$ was accepted as the significance level.

Results

The study encompassed 203 participants, comprising 166 women and 37 men. The mean age was 44.9±10.7 years and 166 (81.8%) were female. BMI, waist, and hip circumference measurements and other demographic data are shown in Table 1. Of the participants, 59 (31%) were diabetic and 63 (29.1%) had a diagnosis of hypertension. The mean UA value of the patients was 5.4±1.3 mg/dL. For the entire study population, the UA level had a median of 5.3 mg/dL.

The mean calculated FRS of the study group was 8.8±8.9. When grouped according to 10-year cardiovascular risk estimates, 138 (68%) were in the low-risk group, 46 (22.7%), in the intermediate risk group, and 19 (9.3%) in the high-risk group.

When the two groups were compared based on the median serum UA value of 5.3 mg/dL, those with serum UA <5.3 mg/dL were defined as group 1 and those with serum UA ≥5.3 mg/dL as group 2. When the 2 groups were compared, there was no significant difference between the FRS (7.8±8.2 vs. 9.8±9.5; p=0.105). The female sex ratio was higher in group 1. Height, waist circumference, systolic and diastolic blood pressure, triglyceride, and insulin levels were significantly lower in group 1 than in group 2 (Table 2).

In correlation analysis, FRS was correlated with age, height, waist circumference, waist/hip ratio, systolic and diastolic blood pressure,

Table 1. Demographic and laboratory features of the study population

	Median (minimum-maximum)	Mean
Age (years)	45 (30-71)	44.9±10.7
Female gender (n, %)	166 (81.8)	
Height (cm)	160 (143-193)	161.4±9.6
Weight (kg)	105 (70-170)	106.3±17.1
Waist circumference (cm)	120 (90-158)	119.9±11.9
Hip circumference (cm)	129 (100-158)	129.1±11.9
BMI (kg/m^2)	40 (30-65)	40.5±5.8
Smoking (n)	66 (32.5)	
Hypertension (n)	63 (31.0)	
Diabetes mellitus (n)	59 (29.1)	
Chronic disease (n)	151 (74.4)	
Systolic blood pressure (mmHg)	120 (90-190)	121.5±12.1
Diastolic blood presure (mmHg)	80 (60-190)	78±10.1
Glucose (mg/dL)	101 (71-312)	110.1±33.6
Total cholesterol (mg/dL)	207 (120-370)	210.3±41.5
Triglyceride (mg/dL)	138 (40-1047)	154.1±93.1
LDL cholesterol (mg/dL)	126.8 (14.4-264.4)	130.6±35.3
HDL cholesterol (mg/dL)	47 (25-90)	49.1±11.7
Insulin (mIU/L)	12.4 (0.7-147.5)	15.1±13.2
Uric acid (mg/dL)	5.3 (2.6-9.7)	5.4±1.3
HbA1c (%)	5.8 (4.9-11.1)	6.0±0.9
FRS (%)	5.7 (0.4-47.6)	8.8±8.9
FRS (<10%)	138 (68%)	
FRS (10-19%)	46 (22.7%)	
FRS (>20%)	19 (9.3%)	

BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, HbA1c: Hemoglobin A1c, FRS: Framingham Risk Score

fasting blood glucose, total cholesterol, LDL cholesterol, triglyceride, and insulin levels, and HbA1c level (Table 3). Serum UA level was significantly correlated with weight, waist circumference, hip circumference, BMI, systolic and diastolic pressure, triglycerides, and insulin levels (Table 3).

Table 2. Comparison of patient groups according to serum uric acid levels <5.3 (mg/dL) and ≥5.3 (mg/dL)

	Group 1, (UA <5.3)	Group 2, (UA ≥5.3)	p
Age (years)	44.9±10	44.8±11.3	0.687[m]
Female gender (n, %)	93	73	<0.001[x2]
Length (cm)	159.7±8.3	163.1±10.5	0.038[m]
Weight (kg)	103.7±16.5	108.9±17.4	0.034[m]
Waist circumference (cm)	118±11.9	121.7±11.7	0.016[m]
Hip circumference (cm)	128.2±12.1	130±11.8	0.285[m]
Waist to hip ratio	0.92±0.06	0.94±0.06	0.032[m]
BMI (kg/m^2)	40.3±6.0	40.7±5.6	0.457[m]
Smoking (n)	66		0.802[x2]
Hypertension (n)	63		0.477[x2]
Diabetes mellitus (n)	59		0.842[x2]
Chronic disease (n)	151		0.779[x2]
Systolic blood pressure (mmHg)	119.3±12.6	123.7±11.2	0.002[m]
Diastolic blood presure (mmHg)	77.5±13.1	78.5±15.8	0.022[m]
Glucose (mg/dL)	113.1±42.4	107.1±21.4	0.454[m]
Total cholesterol (mg/dL)	208.0±40.5	212.5±42.5	0.443[m]
Triglyceride (mg/dL)	146.0±108.4	162.0±73.2	0.008[m]
LDL cholesterol (mg/dL)	130.8±35.5	130.6±35.3	0.976[m]
HDL cholesterol (mg/dL)	50.0±12.4	48.2±11.0	0.482[m]
Insulin (mIU/L)	13.4±15.7	16.9±10.0	<0.001[m]
Uric acid (mg/dL)	4.4±0.6	6.4±0.9	<0.001[m]
HbA1c (%)	6.1±1.0	5.9±0.8	0.185[m]
FRS (%)	7.8±8.2	9.8±9.5	0.105[m]
FRS (<10%)	72	66	
FRS (10-19%)	23	23	0.242[x2]
FRS (>20%)	6	13	

[m]Mann Whitney U, [x2]Chi-square test, UA: Uric acid, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, HbA1c: Hemoglobin A1c, FRS: Framingham Risk Score

In univariate logistic regression analysis of the patient groups, gender, height, weight, waist circumference, hip circumference, systolic pressure, and insulin value were found to be significantly associated with the prediction of serum UA level.

In the multivariate reduced model, height and systolic pressure values were also significantly associated with the prediction of serum UA level (Table 4).

Discussion

The main conclusion of our study is that UA levels, in addition to traditional cardiovascular risk markers and scoring systems, can be used to predict CVD risk in individuals with obesity. The FRS system was found to correlate with UA levels in the studied population.

Table 3. Evaluation of serum uric acid level and Framingham risk scoring by Spearman correlation analysis

	Framingham Risk Score		Uric acid	
	r	p	r	p
Framingham Risk Score			0.200	0.004
Uric acid	0.200	0.004	1	<0.001
Age (years)	0.780	<0.001	0.030	0.669
Lenght (cm)	-0.141	0.045	0.100	0.157
Weight (kg)	-0.009	0.900	0.229	0.001
Waist circumference (cm)	0.223	0.001	0.227	0.001
Hip circumference (cm)	0.043	0.545	0.149	0.034
Waist to hip ratio	0.251	<0.001	0.114	0.107
BMI (kg/m^2)	0.077	0.278	0.173	0.014
Systolic blood pressure (mmHg)	0.556	<0.001	0.274	<0.001
Diastolic blood presure (mmHg)	0.285	<0.001	0.145	0.039
Glucose (mg/dL)	0.517	<0.001	0.116	0.099
Total cholesterol (mg/dL)	0.413	<0.001	0.001	0.992
HDL cholesterol (mg/dL)	-0.010	0.889	-0.103	0.143
LDL cholesterol (mg/dL)	0.338	<0.001	0.213	0.480
Tryglyceride (mg/dL)	0.442	<0.001	0.213	0.002
Insulin	0.140	0.048	0.321	<0.001
HbA1c	0.540	<0.001	-0.012	0.867

BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HbA1c: Hemoglobin A1c

Table 4. Evaluation of the factors affecting serum uric acid levels of patients by logistic regression analysis

	Univariate model			Multivariate model		
	OR	95% CI	p	OR	95% CI	p
Gender	4.62	1.99-10.70	<0.001	1.046	1,013-1,080	0.005
Lenght (cm)	1.04	1.01-1.07	0.014			
Weight (kg)	1.02	1.00-1.04	0.031			
Waist circumference (cm)	1.03	1.00-1.05	0.028			
Hip circumference (cm)	54.01	1.25-100	0.041			
Systolic BP (mmHg)	1.03	1.01-1.06	0.012	1.039	1,012-1,068	0.005
Insulin	1.03	1.00-1.06	0.049			

OR: Odds ratio, CI: Confidence interval, BP: Blood pressure

Obesity is one of the most important health problems in modern societies and has reached alarming levels in developing countries (12). Abdominal obesity increases the secretion of adipokines and insulin resistance, independent of BMI, and leads to the progression of numerous cardiometabolic risk factors (13). Obesity is not only closely associated with diseases such as hypertension, type 2 DM and metabolic syndrome, but is also an important driving factor for hyperuricemia (14,15).

UA is the last oxidation product of endogenous purine metabolism. It is made in the liver and eliminated in the kidney (6). Increased UA levels have been shown to be associated with hypertension, DM, and endothelial dysfunction, which are important risk factors for atherosclerosis (16). Large-scale studies have shown that serum UA is associated with inflammatory markers such as C-reactive protein (CRP) and interleukins (17). Although UA is known to have an antioxidant effect via scavenging free radicals (18), it is still controversial whether UA itself is a traditional cardiovascular risk factor (6). The potent antioxidant effect of urate occurs only at physiologic concentrations (19). In two separate studies, intravenous infusion of UA was shown to improve endothelial function in type 1 DM (20) and healthy adults (21). A separate meta-analysis demonstrated that elevated UA levels independently increased the likelihood of cardiovascular events, beyond the influence of conventional cardiovascular risk factors (22). In a study by Atar et al. (16), it was shown that UA was directly related to coronary calcium score on computed tomography coronary angiography, and as UA levels increased, calcium score also increased. In a study by Huang et al. (3), it was investigated whether CRP, white blood cells and UA levels differed between genders when determining the risk of cardiovascular events, and it was shown that they could only be used in male individuals for this purpose. In our study, similarly, UA levels associated with FRS and higher in males. This is generally compatible with the uricosuric effect of estrogen (23).

In a study conducted on 4,140 patients belonging to the Third Generation Framingham cohort, it was shown that UA levels were associated with femoral and carotid pulse wave velocity, which is an indicator of vascular stiffness (6). In another study conducted by Viazzi et al. (24) on hypertensive individuals with high risk of DM, the relationship of UA with metabolic syndrome and various cardiovascular risk factors was examined, and it was concluded that mild hyperuricemia was an independent indicator of metabolic syndrome in this patient group. In our study, UA levels were correlated with FRS, which is conventionally accepted as a predictor of cardiovascular events.

In another study, the effect of anti-hyperuricemic treatment on the prevalence of CVD in hypertensive patients was investigated. Among 458 hypertensive patients, some received anti-hyperuricemic therapy in addition to hypertension treatment, while others were given only anti-hypertensive therapy. At the end of the study, an increase in the number and dose of anti-hypertensive drugs was observed in the group of patients who did not receive anti-hyperuricemic treatment accompanied by a significant increase in the prevalence of CVD in this group. For patients whose serum UA was considered a variable factor, the variability was attributed to two mechanisms: the inflammatory response induced by serum UA on the smooth muscle cells in blood vessels, and the oxidative stress resulting from reactive oxygen species (25). In the study published by Li et al. (26), the relationship between serum UA level and all-cause and cardiovascular mortality in an obesity population was examined. In this study, 12,637 participants who met the inclusion criteria were prospectively observed for 15 years. While increased levels of serum UA were linked to mortality from all causes, our study found no significant relationship between these levels and deaths due to cardiovascular issues.

It is not a coincidence that the parameters showing the highest correlation with the FRS system in our study group are age, fasting blood glucose, HbA1c, and systolic blood pressure. The primary parameters constituting the FRS system are age, systolic blood pressure, the presence of diabetes, smoking status, total cholesterol, and low-density cholesterol. It is expected that patients with obesity have high atherogenic parameters. These are also the parameters that show the highest correlation with the Framingham Scoring System. Although UA levels are known to be a risk factor for atherosclerosis, a weak correlation between UA levels and the FRS system was found in our study. This may be due to the relatively small size of our study group or the possibility that patients with obesity might be using medications affecting UA levels for their chronic diseases.

Research has explored the connection between elevated serum UA levels and obesity, with findings indicating that obesity may lead to overproduction or inadequate renal elimination. The accumulation of excessive visceral fat causes a substantial influx of plasma free fatty acids into the portal vein and liver. This process triggers triglyceride synthesis resulting in the production of large quantities of UA through the activated UA synthesis pathway (27,28). A separate investigation conducted by Zeng et al. (29) tracked 15,959 individuals, over a 9-year period, determining that elevated levels of serum UA correlated with an increase in obesity. This finding lends support to the results of our research.

Study Limitations

Our study was conducted through a retrospective examination of individuals with obesity who presented to a single center over a certain period. Our UA levels are generally below the widely accepted values. Considering all parameters, the median value of the individuals in the study profile was taken as the threshold. The low significance of the values in the correlation analysis is another limitation of the study, which could be due to the limited number of cases. Our study is limited by the absence of extended patient monitoring. The research could have been more impactful in showcasing the outcomes of the FRS if we had been able to present cardiovascular events observed during their long-term follow-up of the cases.

Conclusion

Serum UA measurement is an easily applicable and inexpensive parameter that can be used as a CVD risk marker in obesity, a disease that has most of the classical CVD risk factors. Although there is not yet a scoring system that can use serum UA level for this purpose, it is obvious that this parameter is associated with many metabolic conditions that predispose to CVD. In this respect, it is thought that serum UA level

monitoring, the importance of which is supported by the literature, may contribute to preventive medicine by being put into practical use in predicting CVD risk in population with obesity, which is known to be at cardiovascular risk due to metabolic dysfunctions, as in our study.

Ethics

Ethics Committee Approval: The study received ethical clearance from University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 1898, date: 28.06.2019).

Informed Consent: All participants provided their informed consent.

Footnotes

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

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D2 Lymphadenectomy and Complete Mesogastric Excision in Gastric Cancer: 5-Year Results from a Single Center

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ABSTRACT

Introduction: Complete mesogastric excision (CME), combined with classical D2 lymphadenectomy (D2LND), ensures the removal of all mesogastric tissue. This procedure aims to reduce local cancer spread and prevent the dissemination of microscopic cancer cells. The aim of this study is to compare CME with conventional D2LND in the treatment of gastric cancer (GC) and to evaluate our five-year results, emphasizing the potential advantages of CME.

Methods: Data on patients who underwent surgery for GC between 2016 and 2021 were collected from the clinical information system. The data from cases undergoing D2 lymph node dissection with CME were compared and retrospectively analyzed.

Results: Among the 76 cases, 41 (54%) underwent D2 dissection in addition to gastric resection, the other while the other 35 (46%) underwent CME. During the three-year follow-up period, recurrence was observed in 12 patients (29.2%) in the D2 dissection group, whereas 4 patients (11.4%) in the CME group experienced recurrence.

Conclusion: By facilitating more extensive lymphadenectomy without increasing postoperative complications, CME may contribute to reducing tumor recurrence. Although preliminary findings support the potential oncological benefits of this technique, further validation through large-scale, multicenter, randomized controlled trials is necessary to establish its definitive clinical utility.

Keywords: Gastric cancer, complete mesogastric excision, lymphadenectomy

Introduction

Except for East Asian countries, where early screening programs are implemented, gastric cancer (GC) is typically diagnosed at an advanced stage (1,2). Therefore, gastrectomy with D2 lymphadenectomy (D2LND) following neoadjuvant therapy remains the standard treatment approach (3,4). However, one of the most significant challenges in these cases is the high recurrence rate. According to studies in the literature, recurrence rates after curative surgery can be as high as 60% (5-8).

In colorectal cancer surgery, Cecil et al. (9) introduced the total mesorectal excision technique, successfully reducing local recurrence rates in rectal cancer from approximately 33% to 10%. Similarly, Hohenberger et al. (10) addressed recurrence in colon cancer by implementing the total mesocolic excision and vascular ligation technique, lowering the five-year recurrence rate from 6.5% to 3.6% and increasing five-year cancer-specific survival from 82.1% to 89.1% in patients undergoing curative resection.

In 2015, Xie et al. (11) introduced the concept of complete mesogastric excision (CME) for GC. The CME technique involves the total removal of the mesogastrium, the connective tissue surrounding the stomach which is considered a potential pathway for cancer cell dissemination. When combined with classical D2LND, CME ensures the complete excision of the mesogastric tissue, aiming to reduce local tumor spread and prevent microscopic cancer dissemination.

Xie et al. (12) reported that the combination of gastrectomy, D2LND, and CME resulted in better short-term outcomes and surgical safety in patients with advanced GC compared to conventional D2LND (13-16). Furthermore, Shinohara et al. (17) and Girnyi et al. (18) proposed that systematic mesogastric excision in GC should align with the surgical principles of total mesorectal excision in rectal cancer and complete mesocolic excision in colon cancer. These researchers advocated for the en bloc resection of the mesogastrium while preserving the relevant vessels in the pancreas and mesogastrium to achieve D2LND based on the CME concept.

Within this framework, despite the anatomical limitations specific to the mesogastrium, D2 gastrectomy can be considered a form of mesentery-based surgery. Similar to total mesorectal excision and complete mesocolic excision, the CME principle is expected to contribute to the standardization of surgical strategies for GC.

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The aim of this study is to compare CME with conventional D2LND in the treatment of GC and to evaluate our five-year results, emphasizing the potential advantages of CME.

Methods

In this study, data from patients who underwent surgery for GC at the Surgical Oncology Clinic of the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, between June 2016 and 2021, were retrospectively reviewed. The study was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Ethics Committee (approval number: 2022/304, date: 29.09.2022).

Patient Selection and Group Classification

Patients included in the study were categorized into two distinct groups based on the surgical technique employed. Those who underwent conventional gastrectomy with standard D2LND were referred to as the control group, while those who underwent gastrectomy with D2LND in conjunction with CME constituted the study group. This classification allowed for a comparative evaluation of the oncological and perioperative outcomes associated with the two surgical approaches.

Study Parameters and Variables

The study comprehensively assessed various preoperative, intraoperative, and postoperative parameters, including age, gender, body mass index (BMI), and American Society of Anesthesiologists (ASA) classification scores. Type of gastrectomy performed (total or subtotal), tumor location (cardia, antrum, corpus), and pathological TNM (pTNM) staging. Chemotherapy and/or radiotherapy may be administered before or after surgery. Operative time, estimated intraoperative blood loss, number of lymph nodes dissected, and achievement of R0 resection (negative surgical margins). Morbidity and mortality rates, occurrence of surgical complications, length of hospital stay, and time to initiation of oral intake are key variables in assessing patient outcomes. Recurrence rates, disease-free survival (DFS), and overall survival (OS).

To ensure the homogeneity of the study cohort and minimize potential confounders, some patients were excluded from the study. The excluded patients were as follows: emergency surgical intervention due to tumor-related complications such as bleeding or obstruction, presence of distant metastases or intraperitoneal peritoneal carcinomatosis at the time of diagnosis, undergoing palliative rather than curative-intent surgery. Incomplete medical records or loss to follow-up within the first postoperative year.

Surgical Technique

The CME procedure was meticulously performed by experienced surgeons who specialize in GC surgery. The technique focused on the en bloc resection of the mesogastrium to minimize the risk of tumor cell dissemination along anatomical lymphovascular pathways. CME was executed in three principal anatomical regions: 1. Lower pyloric region - ensuring precise dissection around the duodenal stump and right gastroepiploic vascular structures. 2. Splenic region - addressing lymphatic drainage pathways associated with the splenic artery and hilum. 3. Upper pancreatic region - preserving critical pancreatic structures while achieving comprehensive lymphadenectomy. Further stratification of the mesogastric dissection areas classified CME into six distinct subgroups: right gastroepiploic, right gastric, left gastric, posterior gastric, left gastroepiploic, short gastric mesentery. The meticulous adherence to these surgical principles was aimed at improving oncological clearance while minimizing perioperative morbidity.

Statistical Analysis

All statistical analyses were performed using SPSS version 20.0 software (IBM SPSS, Inc., Chicago, IL, USA. Continuous variables were presented as mean ± standard deviation for normally distributed data. Categorical variables were summarized using absolute frequencies and percentages. Comparative analyses between the two surgical groups were conducted based on the nature of the variables. A p-value of <0.05 was considered statistically significant in all analyses.

Results

Between June 2016 and 2021, 121 patients were operated on due to GC in our clinic. Among these 121 patients, 45 were excluded due to prior gastric surgery, stage 4 disease, or incomplete data. Consequently, 76 patients were included in the study. Among them, 41 (54%) underwent gastrectomy with D2LND, while 35 (46%) underwent gastrectomy with D2LND combined with CME.

In the gastrectomy + D2LND group, 30 patients underwent total gastrectomy (73%) and 11 patients (27%) underwent subtotal gastrectomy. In the D2 + CME group, total gastrectomy was performed in 28 patients (80%) and subtotal gastrectomy in 7 patients (20%) (p=0.48). The gastrectomy + D2LND group comprised 23 male (56%) and 18 female (44%) patients, while the D2 + CME group included 20 male (57.2%) and 15 female (42.8%) patients (p=0.91).

The mean age was 62.92±7.60 years in the gastrectomy + D2LND group and 61.30±8.12 years in the D2 + CME group (p=0.43). The mean BMI was 24.30±2.83 kg/m^2 in the gastrectomy + D2LND group and 25.23±2.81 kg/m^2 in the D2 + CME group (p=0.27). In terms of age, gender, BMI, ASA scores, surgical method (total/subtotal gastrectomy), tumor location (cardia, antrum, corpus), or pTNM stage (p>0.05), there was not a statistically significant difference between the two groups (Table 1).

In the gastrectomy + D2LND group, total gastrectomy was performed in 28 patients (68.3%), distal gastrectomy in 12 patients (29.3%), and proximal gastrectomy in 1 patient (2.4%). In the D2 + CME group, total gastrectomy was performed in 23 patients (65.7%), distal gastrectomy in 11 patients (31.4%), and proximal gastrectomy in 1 patient (2.9%). R0 resection with negative surgical margins was achieved in all patients in both groups. Positive tumor deposits (TD) were identified in 17 patients (41.4%) in the D2LND group and in 14 patients (40%) in the D2 + CME group (p=0.88). No statistically significant differences were noted between the groups in terms of positive TD rates, number of positive lymph nodes, or postoperative hospital stay (p>0.05).

Although the operation duration was significantly longer in the D2 + CME group compared to the D2LND group [220.40±41.23 minute

Table 1. Demographic datas			
Variable	**Group A (D2LND), (n=41)**	**Group B (D2 + CME), (n=35)**	**p**
Male/female, (n)	23/18	20/15	0.91
Mean age (years)	62.92±7.60	61.30±8.12	0.43
Mean body mass index (kg/m^2)	24.30±2.83	25.23±2.81	0.27
ASA score, n (%)			0.83
ASA I	15 (36.5%)	14 (40%)	
ASA II	12 (29.2%)	11 (31.4%)	
ASA III	9 (21.9%)	7 (20%)	
ASA IV	5 (12.1%)	3 (8.6%)	
Tumor location, n (%)			0.78
Cardia	15 (36.5%)	12 (34.2%)	
Antrum	16 (39.0%)	13 (37.1%)	
Corpus	10 (24.5%)	10 (28.7%)	
Surgical method, n (%)			0.48
Total gastrectomy	30 (73%)	28 (80%)	
Subtotal gastrectomy	11 (27%)	7 (20%)	
Positive tumour deposits, n (%)	17 (41.4%)	14 (40%)	0.88

Group A: Patients underwent gastrectomy + D2LND, Group B: Patients underwent gastrectomy + D2LND + CME. ASA: American Society of Anesthesiologists, D2LND: D2 lymph node dissection, CME: Complete mesogastric excision

Table 2. Intraoperative and postoperative findings			
Variable	**Group A (D2LND), (n=41)**	**Group B (D2 + CME), (n=35)**	**p**
Duration of operation, minute	175.44±51.39	220.40±41.23	**<0.001**
Intraoperative blood loss, mL	130.47±56.64	120.21±47.30	0.43
Mean number of dissected lymph nodes	36.37±14.71	44.15±13.5	**<0.001**
Time to first bowel movement, days	3 (2-4)	3 (2-4)	0.82

Group A: Patients who underwent gastrectomy + D2LND, Group B: Patients who underwent gastrectomy + D2LND + CME. D2LND: D2 lymph node dissection, CME: Complete mesogastric excision

(min.) vs. 175.44±51.39 min., p<0.001], intraoperative blood loss was comparable (120.21±47.30 mL vs. 130.47±56.64 mL, p=0.43). Additionally, the number of harvested lymph nodes was significantly higher in the D2 + CME group (44.15±13.5 vs. 36.37±14.71, p<0.001). The time to first bowel gas passage and initiation of a liquid diet was similar between the groups [D2 group: 3 (2-4) days vs. D2 + CME group: 3 (2-4) days, p=0.82] (Table 2).

According to the complication classification, no significant difference was observed in postoperative complications between the D2LND and D2 + CME groups (p=0.79). No perioperative mortality occurred in either group (Table 3). The most common postoperative complications were pulmonary infections, ileus, and surgical site infections, occurring in 8 patients (19.51%) in the D2LND group and in 7 patients (20%) in the D2 + CME group, with no statistically significant difference between groups (p=0.79).

The mean follow-up period was 36 months. During the three-year follow-up, eight patients (19.5%) in the D2LND group were lost to follow-up, and recurrence was observed in 12 patients (29.2%). In the D2 + CME group, 4 patients (11.4%) were lost to follow-up, and recurrence was detected in 4 patients (11.4%). The local recurrence rate was higher in the D2LND group (29.26%) compared to the D2 + CME group (11.42%), and it was statistically significant (p=0.04) (Table 4).

Table 3. Mortality and morbidity			
Variable	**Group A (D2LND), (n=41)**	**Group B (D2 + CME), (n=35)**	**p**
Clavien-Dindo Classification			0.79
Grade 1	5	4	
Grade 2	3	3	
Grade 3	0	0	
Grade 4	0	0	
Perioperative mortality	0	0	1.00

Group A: Patients underwent gastrectomy + D2LND, Group B: Patients underwent gastrectomy + D2LND + CME. D2LND: D2 lymph node dissection, CME: Complete mesogastric excision

The three-year OS and DFS rates in the D2LND group were 73.1% (30/41) and 68.2% (28/41), respectively. In the D2 + CME group, the 3-year OS and DFS rates were 74.2% (26/35) and 68.5% (24/35), respectively (p=0.88, p=0.97) (Figure 1).

Discussion

Given the high recurrence rates following GC surgery, it is imperative to refine surgical techniques, implement strategies to minimize perioperative cancer cell dissemination, and ensure adherence to

Table 4. Follow-up findings

Variable	Group A (D2LND), (n=41)	Group B (D2 + CME), (n=35)	p
Number of patients lost to follow-up	8 (19.5%)	4 (11.4%)	0.34
Number of patients with recurrence	12 (29.2%)	4 (11.4%)	**0.04**
Overall survival rate	73.1%	74.2%	0.88
Disease free survival rate	68.2%	68.5%	0.97

Group A: Patients underwent gastrectomy + D2LND, Group B: Patients underwent gastrectomy + D2LND + CME. D2LND: D2 lymph node dissection, CME: Complete mesogastric excision

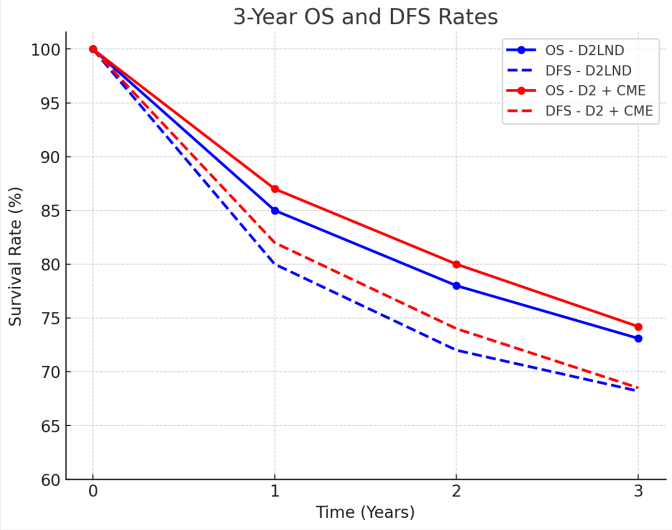

Figure 1. Three-years OS and DFS rates. Group A: Patients underwent gastrectomy + D2LND, Group B: Patients underwent gastrectomy + D2LND + CME, Blue lines: D2LND group (solid line: OS, dashed line: DFS), Red lines: D2 + CME group (solid line: OS, dashed line: DFS)
OS: Overall survival, DFS: Disease-free survival, D2LND: D2 lymp node dissection, CME: Complete mesogastric excision

standardized postoperative treatment and follow-up protocols (19). Recurrence may result from various factors, including lymphatic metastasis, vascular trauma during lymphadenectomy, peritoneal dissemination, and tumor cell infiltration within intramesenteric dissectable layers. Recently, research has increasingly focused on the role of CME in controlling disease progression and metastasis pathways. Xie et al. (11) introduced CME as an adjunct to D2 gastrectomy, conceptualized as the "Table Model," with the primary objective of reducing intraoperative cancer cell dissemination and improving long-term oncological outcomes compared to conventional D2 gastrectomy. While D2 + CME has been associated with a lower presence of free intraperitoneal cancer cells and enhanced DFS, concerns regarding its safety and overall efficacy remain unresolved (13,14).

Xie et al. (19) conducted a randomized controlled trial comparing D2 + CME and conventional D2 gastrectomy in 486 patients. Their findings indicated that D2 + CME was associated with reduced intraoperative blood loss, more extensive lymph node dissection, and superior short-term outcomes, particularly in patients with advanced GC (19). Granieri et al. (20) further demonstrated that CME led to decreased intraoperative blood loss, shorter operative times, earlier return of bowel function, and reduced hospital stays, with no significant differences in postoperative complications. Similarly, Cao et al. (21) observed reduced blood loss in laparoscopic D2 + CME procedures compared to the standard D2 approach. In a retrospective analysis of 599 cases of locally advanced GC treated surgically between 2014 and 2019, Li et al. (22) found no statistically significant difference between D2 and D2 + CME groups regarding mesogastric TD, pathological lymph node counts, or length of hospital stay ($p>0.05$). However, the D2 + CME cohort exhibited reduced intraoperative bleeding, earlier postoperative bowel function recovery, and significantly higher lymph node yields. Importantly, laparoscopic D2 + CME did not increase postoperative complications (22). Our findings align with Li et al. (22) conclusions regarding TD, yet we observed longer operative times in the D2 + CME group. Unlike the studies by Li et al. (22), Cao et al. (21), and Granieri et al. (20), our study found no significant difference in intraoperative blood loss between D2 and D2 + CME groups (120.21±47.30 mL vs. 130.47±56.64 mL, $p>0.05$). Additionally, the time to first bowel movement and liquid diet initiation remained comparable between the groups.

The extent of lymph node dissection is a critical determinant of GC surgical outcomes. Granieri et al. (20) demonstrated that CME facilitated more comprehensive lymphadenectomy compared to conventional D2 gastrectomy. Xie et al. (23) reported a significantly greater lymph node yield with D2 + CME than with standard D2 gastrectomy (34 vs. 27 nodes, respectively). Similarly, Cao et al. (21) reported a median of 31 resected regional lymph nodes in patients undergoing laparoscopic subtotal gastrectomy with D2 + CME. Consistent with these findings, our study observed a significantly higher lymph node yield in the D2 + CME cohort.

Zhao et al. (24) conducted an observational cohort study between 2013 and 2017, comparing D2 and D2 + CME procedures in 855 patients. Their results indicated that D2 + CME was associated with reduced blood loss, higher lymph node dissection counts, and expedited bowel function recovery, suggesting superior short-term outcomes compared to conventional D2 dissection in resectable GC cases (24). Cai et al. (25) examined 323 patients with T1-3N0M0 GC, who underwent D2 + CME (n=185) or standard D2 gastrectomy (n=138) between 2014 and 2018. They reported lower intraoperative blood loss, increased lymph node retrieval, and faster postoperative recovery in the D2 + CME group, with no significant difference in postoperative morbidity (25). Additionally, Li et al. (22) found no significant differences in complication rates between D2 + CME (20.7%) and D2 (19.4%) groups ($p>0.05$). Cao et al. (21) observed a postoperative morbidity rate of 9.3% and no perioperative mortality in patients undergoing D2 + CME, with comparable hospitalization durations to the standard D2 approach. Xie et al. (19) reported prolonged operative times in the D2 + CME cohort but no increase in adverse events. Cai et al. (25) found a significantly lower local recurrence rate in the D2 + CME group ($p=0.031$), with 5-year DFS rates of 95.6% and 90.4% in the D2 + CME and D2 groups, respectively.

Duzkoylu et al. (26) conducted a prospective randomized study in 37 cases, comparing CME with conventional surgical techniques in terms of short-term outcomes. Their findings suggested that CME led to reduced intraoperative blood loss significantly higher numbers of retrieved

lymph nodes, and improved DFS compared to standard D2 gastrectomy, establishing CME as a safe and oncologically advantageous technique (26). Xie et al. (23) further evaluated the impact of D2 + CME on survival in the DCGC01 trial (2014-2018). Among 169 patients in each cohort, recurrence was reported in 50 (29.6%) of the D2 group and 33 (19.5%) of the D2 + CME group (p=0.032) (23). In concordance with existing literature, our study found no statistically significant difference between D2 and D2 + CME regarding the severity of postoperative complications (p>0.05); and no perioperative mortality was reported in either group.

Study Limitations

The primary limitations of this study include its retrospective design and the predominance of comparative data derived from Chinese cohorts. Additionally, the lack of Western and European data on CME, as well as the heterogeneity of cases due to variations in neoadjuvant treatment protocols and demographic characteristics, remains significant constraints.

Conclusion

The integration of CME with D2LND represents a promising advancement in GC surgery. By facilitating more extensive lymphadenectomy without increasing postoperative complications, CME may contribute to reducing tumor recurrence. Although preliminary findings support the potential oncological benefits of this technique, further validation through large-scale, multicenter, randomized controlled trials is necessary to establish its definitive clinical utility.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Ethics Committee (approval number: 2022/304, date: 29.09.2022).

Informed Consent: Retrospective study.

Footnotes

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

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Comparison of Platelet Indices in Patients with Obstructive Sleep Apnea and Obstructive Lung Diseases + Obstructive Sleep Apnea Syndrome

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ABSTRACT

Introduction: We aimed to observe the changes in platelet activities in patients with obstructive sleep apnea (OSA) and obstructive lung diseases + obstructive sleep apnea (OLDOSA) syndrome.

Methods: Adult patients who were followed up with the diagnosis of OSA and OLDOSA syndrome between 06.2018-06.2020 in our clinic were evaluated retrospectively. Changes in platelet indices were investigated.

Results: Of the 354 cases included in the study, 240 were male (67.7%) and 114 were female (32.3%). The control group (simple snoring) included 53 patients, the OSA group included 230 patients, and the OLDOSA group included 71 patients. The groups showed similarities in relation to gender (p=0.407). When the mean platelet volume (MPV) and platelet distribution width (PDW) values were evaluated, a significant discrepancy was noted among the different groups (p=0.01, p=0.02, respectively), enhancing coherence. A notable disparity was observed among the groups with regard to cardiovascular diseases (p=0.00).

Conclusion: In our study, we found that MPV and PDW values increased in patients with OSA and OLDOSA syndrome compared to the control group in patients with OSA and OLDOSA syndrome. MPV was found to be significantly higher in the OLDOSA group compared to the OSA group. We think that these parameters may be indicators of increased cardiovascular risk in patients with OSA and OLDOSA syndrome.

Keywords: Obstructive sleep apnea, OLDOSA syndrome, platelet indices

Introduction

Overlap syndrome describes the association of obstructive sleep apnea (OSA) and other pulmonary diseases [asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, and cystic fibrosis]. The association of obstructive lung diseases, namely COPD and asthma, with OSA has been defined as obstructive lung diseases + OSA (OLDOSA) syndrome (1).

The co-existence of COPD + OSA is common, and it has been suggested that the reason is the similarity of the risk factors identified for both diseases. Therefore, investigating the presence of COPD in OSA patients and investigating OSA symptoms and findings in COPD patients will enable the diagnosis of cases with overlap syndrome (2). The co-existence of OSA and COPD has a clinically more severe course compared to when each disease is observed alone (3). Considering the high prevalence of both COPD and OSA, overlap syndrome is expected in 29% of OSA patients (4).

Another obstructive lung disease associated with OSA is asthma. In the association between OSA and asthma, sleep apnea may provoke asthma attacks. In asthmatic patients, nocturnal bronchospasm can lead to sleep disturbances and hypoxemia. Therefore, the number of arousals is higher and nocturnal hypoxemia is observed more severely in patients with OSA + asthma association (5). A large meta-analysis in 2017 reported that 49.5% of asthma patients had OSA and that asthma patients were 2.64 times more likely to have OSA than controls (6). In patients with asthma and COPD, complications with OSA, as well as airway obstruction, become more pronounced.

Platelets play an important role in atherosclerotic plaque formation, progression of atherosclerosis, and thrombosis. Platelets express and secrete substances involved in the process of inflammation, coagulation, thrombosis, and atherosclerosis (7). In addition, platelet activation has been associated with cardiovascular morbidity (8).

Mean platelet volume (MPV) and platelet distribution width (PDW) are biomarkers of platelet activation (9,10). Increased MPV is a harbinger of cardiovascular disease (CVD), including cerebrovascular and coronary artery disease. It has also been associated with the presence of obesity,

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diabetes mellitus (DM), and metabolic syndrome (11,12). During an inflammatory response, there is an increase in platelet count and platelet swelling, both of which can affect PDW. PDW is increased by changes in platelet morphology and size that occur in inflammatory states (13). In patients with OSA, increased systemic inflammation has been identified, while chronic inflammation has also been described in patients with COPD and asthma (14,15).

Our study was planned to compare platelet activities in patients with OSA and OLDOSA syndrome.

Methods

The study was conducted between 01.06.2018-08.06.2020 in patients who underwent polysomnography (PSG) as a result of evaluations for sleep apnea in the chest diseases outpatient clinic. The demographic data, smoking history, comorbidities, body mass index (BMI), complete blood parameters taken at first admission, lipid profiles and diagnostic PSG results of three groups [OSA, OLDOSA syndrome and control group (apnea-hypopnea index (AHI) <5] were analyzed. Informed consent was obtained from the patients participating in the study. Patients with a history of hematologic disorder or malignancy or anomalous hematocrit, abnormal white blood cell count and/or abnormal platelet count were excluded. After the present evaluations, we aimed to examine platelet indices in patients with OSA, and OLDOSA syndrome. Ethical approval for this study was obtained from the Balıkesir University Clinical Research Ethics Committee (approval number: 2022/107, date: 28.09.2022).

Statistical Analysis

All analyses were performed using SPSS version 23.0. Numerical variables with normal distribution were defined as mean ± standard deviation, and those with non-normal distribution were defined as median (minimum-maximum) Categorical variables were expressed as numbers (percentage). Normality analysis between the groups was performed with the Kolmogorov-Smirnov test. The chi-square test was used to evaluate categorical data. In comparing more than two independent groups, the Kruskal-Wallis test was used for variables that were not normally distributed; the One-Way ANOVA test was used for normally distributed variables; and multiple comparison tests (post-hoc) were used to identify differences between significant groups. According to the Levene's test result, the variances of the groups were considered to be homogeneous, and the Scheffé's test was applied. A critical α value of 0.05 was considered significant.

Results

Of the 354 cases admitted to the study, 240 were male (67.7%) and 114 were female (32.3%). The control group (simple snoring) comprised 53 patients, the OSA group comprised 230 patients, and the OLDOSA group comprised 71 patients (27 with COPD, 44 with asthma). When the groups were evaluated according to gender, a similarity was detected between the groups (p=0.74) (Table 1). When the age of the groups was evaluated, a significant difference was found between them (p=0.00) (Table 1).

While the prevalence of smoking history was highest among individuals in the OLDOSA group (60.6%), no statistically significant variance was observed among the groups (p=0.34) (Table 1). The prevalence of

Table 1. General characteristics of patient groups

	Controls, (n=53)	OSA, (n=230)	OLDOSA, (n=71)	p
Age	48.53±10.39	51.74±11.57	56.94±11.52	**0.00**
Gender, (%)				
Male	34 (64.2)	159 (69.1)	47 (66.2)	0.74
Female	19 (35.8)	71 (30.9)	24 (33.8)	
Smoking, (%)				
Yes	24 (45.3)	99 (43)	43 (60.6)	0.34
No	29 (54.7)	131 (57)	28 (39.4)	
Comorbidity, (%)				
Yes	24 (45.3)	162 (70.4)	62 (87.3)	**0.00**
No	29 (54.7)	68 (29.6)	9 (12.7)	
Diabetes mellitus (%)				
Yes	9 (17)	84 (36.5)	32 (45.1)	**0.00**
No	44 (83)	146 (63.5)	39 (54.9)	
Hypertension, (%)				
Yes	17 (32.1)	125 (54.3)	41 (57.7)	**0.00**
No	36 (67.9)	105 (45.7)	30 (42.3)	
CVD, (%)				
Yes	6 (11.3)	58 (25.2)	29 (40.8)	**0.00**
No	47 (88.7)	172 (74.8)	42 (59.2)	

CVD: Cardiovascular disease, OSA: Obstructive sleep apnea, OLDOSA: Obstructive lung diseases + obstructive sleep apnea

smoking history was notably greater in the OLDOSA group than in the simple snoring and OSA groups (p=0.01).

When assessed based on the existence of comorbidities, a notable distinction was observed among the groups (p=0.00). Comorbidities were mostly observed in the OLDOSA group (87.3%).

The disparity in prevalence rates of DM and hypertension (HT) showed statistical significance across all groups (p=0.00 and p=0.00, respectively) (Table 1). In subgroup analysis, a significant difference in DM and HT was found in the OSA and OLDOSA groups compared to the control group (p=0.03 and p=0.03, respectively). In addition, although DM and HT were more common in the OLDOSA group than in the OSA group, no significant difference was found between the groups (p=0.21 and p=0.68, respectively).

The prevalence of CVD was 11.3% in the control group, 25.2% in the OSA group, and 40.8% in the OLDOSA group. During the assessment of CVD, a noteworthy difference was detected among all groups (p=0.00) (Table 1). A statistically significant difference was observed in the OSA and OLDOSA groups compared to the control group (p=0.00). Additionally, the OLDOSA group displayed a markedly elevated occurrence of CVD when contrasted with the OSA group (p=0.01).

Among all patients, 66 patients (18.6%) had hyperlipidemia, 11 patients (3.1%) had endocrine system disease (other than DM), 18 patients (5%) had psychiatric disease, 15 patients (4.2%) had urologic disease, 8 patients (2.2%) had rheumatologic disease and 9 patients (2.5%) had neurologic disease.

When BMI was divided into categories of 30 and above, and below 30, a statistically significant difference was found among the groups (p<0.01) (Table 2). A significant difference was detected between the patient group and the control group (p<0.01). Although there were more obese patients in the OLDOSA group, compared to the OSA group, no significant difference was found between them (p=0.21).

A notable disparity was observed in the hemoglobin and hematocrit values among the groups (p=0.02, p=0.04, respectively) (Table 2). Platelet counts showed no significant variation among the groups (p=0.91).

The mean value of MPV was determined as 8.60±1.20 in the control group, 8.72±1.13 in the OSA group and 9.15±1.39 in the OLDOSA group, and a notable discrepancy was observed among the groups (F=4.23, p=0.01) (Table 2). In the post-hoc analysis, it was identified that the mean MPV level in the OLDOSA group showed a significant increase compared to both the simple snoring group (X=0.54) and the OSA group (X=0.43).

When the effectiveness of MPV for CVD was evaluated, the AUC value was found to be 0.522 in the receiver operating characteristic analysis and not statistically significant (p=0.53).

A remarkable difference was detected among the groups in relation to the PDW median value (p=0.02) (Table 2). When conducting pairwise comparisons among the groups, it was observed that the PDW value exhibited a statistically significant increase in the OSA and OLDOSA groups compared to the group with simple snoring (p=0.02, p=0.01). There was no discernible discrepancy between the OSA and OLDOSA groups (p=0.307).

When comparing the different groups with regard to red cell distribution width and plateletcrit, no statistically significant variance was detected (p=0.32, p=0.77).

A notable distinction was observed among the groups with regard to minimum oxygen saturation, mean oxygen saturation, and the oxygen

Table 2. Age, body-mass index and platelet index of the patient groups

		Controls, (n=53)	OSA, (n=230)	OLDOSA, (n=71)	p
Body mass index	<30	29 (54.7%)	63 (27.4%)	14 (19.7%)	**0.00**
	≥30	24 (45.3%)	167 (72.6%)	57 (80.3%)	
Hemoglobin, g/dL		14.3±1.68	14.3±1.62	13.6±1.72	**0.02**
Hematocrit, (%)		42.8±4.53	42.8±4.47	41.2±5.03	**0.04**
Platelet, (%)		260.91±63.53	265.15±67.18	266.14±80.87	0.91
MPV, (%)		8.60±1.20	8.72±1.13	9.15±1.39	**0.01**
PDW (min.-max.)		16.40 (9.8-19.9)	16.50 (8.6-20)	16.70 (7.9-19.2)	**0.02**
Pct (min.-max.)		0.22 (0.09-0.35)	0.22 (0.10-0.48)	0.23 (0.10-0.38)	0.77
RDW (min.-max.)		13.60 (11-30.2)	13.61 (10.5-28.1)	13.96 (11.9-25.9)	0.32
Total colesterol		192.32±36.93	200.70±42.34	190.41±34.93	0.23
HDL		46.57±8.24	45.11±9.35	44.37±8.99	0.54
LDL		117.53±35.86	117.38±33.90	117.27±31.20	0.99
AHI score (min.-max.)		2.80 (0.10-4.9)	29.45 (5.2-105)	23 (5.4-89.5)	**0.00**
Min. O_2 sat (min.-max.)		94.55 (91.70-98)	92.94 (77-86)	93 (86-96.05)	**0.00**
Average O_2 sat (min.-max.)		89.75 (74-96)	82.12 (50-94)	82.91 (53-91)	**0.00**
ODI (min.-max.)		2.75 (0.0-52.2)	26.65 (0.5-111.20)	19 (2-84.2)	**0.00**

OSA: Obstructive sleep apnea, OLDOSA: Obstructive lung diseases + obstructive sleep apnea, MPV: Mean platelet volume, PDW: Platelet distribution width, Pct: Plateletcrit, RDW: Red cell distribution width, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, min.: Minimum, max.: Maximum

desaturation index (p=0.00, p=0.00 and p=0.00, respectively) (Table 2). In addition, a significant rise was seen in the patient cohorts in contrast to the control group (p=0.00, p=0.00, and p=0.00, respectively). No significant relationship was detected between these parameters and MPV, and PDW.

No significant disparity was detected among all patients regarding total cholesterol, high-density lipoprotein, and low-density lipoprotein levels in the 226 patients for whom data were accessible (p=0.23, p=0.54, p=0.99, respectively) (Table 2).

Upon analysis of the groups in accordance with the AHI, a significant disparity was identified among the groups (p=0.00).

Discussion

OSA is a disease characterized by recurrent episodes of full (apnea) or partial (hypopnea) upper respiratory tract obstruction during sleep (14). Its prevalence was reported to be 17% in women and 34% in men between the ages of 30-70 (16). Asthma and COPD are common chronic respiratory disorders and are important causes of impaired quality of life, disability and death worldwide (17,18). The presence of COPD and asthma with OSA separately or together has been defined as OLDOSA syndrome (1). These associations may aggravate the course of OSA by leading to chronic hypoxemia, sympathetic activation, subclinical inflammation, pulmonary HT, and cor pulmonale (19).

Asthma, COPD, and OSA share common risk and aggravating factors such as old age, obesity, smoking, and gastroesophageal reflux. It has been reported that the prevalence of OSA increases in the 40-65 age group and decreases after the age of 65 (20,21). In our study, the mean age was 51.7 years in the OSA group; 55.8 years in the OLDOSA group, and was found to be compatible with the literature. Smoking, a prevalent risk factor for the aforementioned conditions, did not show a statistically significant discrepancy across the groups. However, individuals within the OLDOSA cohort demonstrated a significantly greater smoking history compared to the other two groups. The rise seen within the OLDOSA cohort might be understood through the connection between smoking and the development of obstructive respiratory conditions.

OSA is known to play a role in the etiology of DM (22). According to Karakoç et al. (23), the frequency of DM was found to be 3.8% in patients with simple snoring and 12% in patients with severe OSA. A study conducted in Italy reported that DM was more common in patients with COPD than in the general population. The prevalence was 10.5% in the general population and 18.7% in patients with COPD, compared with people without COPD (24). A recent review observed that asthma and DM are two common chronic conditions that frequently coexist (25). In our investigation, a significant discrepancy in the prevalence of DM was noted among the different groups. A significant difference in the measured variable was detected in patient groups compared to the control group. DM was observed at the highest rate in the OLDOSA group, while no significant difference was detected between the OLDOSA and OSA groups for other variables. We believe that this elevation can be explained by the co-existence of diseases.

A history of sleep apnea is present in 35-40% of hypertensive patients and HT in approximately 50% of those with sleep apnea (26). In their meta-analysis, Xu et al. (27) provided evidence that the frequency of HT was increased in individuals with overlap syndrome in comparison to those with either COPD or OSA separately (28). In a study conducted in middle-aged asthmatic subjects, it was shown that the risk of HT increased as FEV_1 decreased (29). In our investigation, the occurrence of HT exhibited notable disparities among the groups. A significant difference was observed in patient groups compared to the control group. Due to the co-existence of diseases, the highest incidence rate was in the OLDOSA group, consistent with the literature. However, no significant difference was found between OLDOSA and the OSA group.

Diseases such as heart failure, cerebrovascular disease, atrial fibrillation, coronary artery disease and HT are strongly associated with OSA (30). The main events involved in this relationship are increased sympathetic activation, oxidative stress, vascular inflammation, endothelial dysfunction, arterial stiffening, and hypercoagulation, which can be triggered by sleep fragmentation and intermittent hypoxia. With effective treatment of OSA, the increased risk burden for CVD can be eliminated (27). The variation in CVD prevalence was noticeable across all groups. Additionally, a significantly higher prevalence was noted in the OLDOSA group compared to the OSA group. We anticipate that both the presence of OSA in the etiology and the frequent occurrence of cardiovascular comorbidities in airway diseases explain this situation.

Obesity plays a role as a predisposing factor for various diseases such as OSA, obesity hypoventilation syndrome, asthma, pulmonary HT, pneumonia, and acute respiratory distress syndrome. There is also evidence of a strong relationship between COPD and obesity (31,32). In a study, the prevalence of obesity in COPD patients was reported to be 18% (33). Obesity is observed in 70% of patients with OSA (34). It has been shown that 36% of adult asthmatics are obese and have a later-onset asthma phenotype (35). In our study, obesity was found to be significantly higher in the OSA and OLDOSA groups compared to the control group. This phenomenon may be explained by the prevalence of obesity as a shared risk factor in the pathogenesis of these conditions. Although obesity was observed at a higher rate in the OLDOSA group compared to the OSA group, no significant difference was found between them.

Several investigations have demonstrated heightened platelet activation and aggregation among individuals diagnosed with OSA (36-38). Hypoxia along with chronic inflammation can trigger platelet activation (39,40). There are different studies reporting a relationship between MPV, which is one of the activation markers, and sleep apnea (41,42). Archontogeorgis et al. (43) demonstrated an increase in MPV among individuals diagnosed with overlap syndrome (COPD + OSA) in comparison to the control group. Furthermore, it was observed that MPV was higher in patients with overlap syndrome compared to the OSA group (43). In another study evaluating the relationship between OSA and MPV, Sarioglu et al. (44) found no significant relationship. In our study, MPV values exhibited notable variations across all the groupings. Furthermore, there was a marked elevation in the OLDOSA group in relation to the OSA group. We hypothesize that these results explain the highest level of platelet activation in the OLDOSA group, due to the co-existence of the diseases. Minimum oxygen saturation and average oxygen saturation, which are indicators of hypoxia, were found to be

significantly lower in the patient groups than in the control group. These results support the finding that platelet activation is high in the OSA and OLDOSA groups.

PDW is an index of platelet volume heterogeneity and may increase in the activation of platelets (45). Some authors reported that MPV and PDW increased in OSA and showed a positive correlation after controlling for possible confounding factors (46). Białas et al. (47) demonstrated a correlation between increased PDW and reduced survival rates in patients diagnosed with COPD. Archontogeorgis et al. (43) showed that the PDW value was significantly higher in patients with OSA and overlap syndrome compared to controls. Our research revealed a notable variance in the PDW value across all the groups. A notable disparity was identified, particularly when comparing the groups of patients and the control group. This result was consistent with studies in the literature. We observed that the PDW value was even higher in the OLDOSA group, where two diseases leading to platelet activation coexist.

Study Limitations

Our research encountered certain constraints. The sample size of patients involved was restricted, potentially impacting the study's ability to identify any existing effects. Furthermore, given the retrospective nature of our observational study, one must acknowledge the possibility of unaccounted confounding variables influencing the outcomes.

Conclusion

Both OSA and OLDOSA syndrome are correlated with elevated platelet activation leading to an increased risk of thrombosis. Patients with OLDOSA syndrome may face an elevated susceptibility to thrombosis as a result of the correlation between OSA and obstructive pulmonary disease. It is our contention that MPV and PDW, recognized as markers of platelet activation, ought to be regarded as viable assessment tools for CVD within this particular patient cohort. Therefore, we think that by including MPV and PDW in clinical evaluation, possible increased disease risks can be detected earlier and the disease burden can be reduced. This is the first study to evaluate platelet activation in OLDOSA syndrome. There is a need for research with a larger population to evaluate the association of MPV and PDW with increased cardiovascular risk in these patients.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Balıkesir University Clinical Research Ethics Committee (approval number: 2022/107, date: 28.09.2022).

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

Footnotes

Authorship Contributions: Surgical and Medical Practices - M.Ç., H.Ç., N.S., G.D.A., F.E.; Concept - M.Ç., H.Ç., N.S., F.E.; Design - M.Ç., H.Ç., N.S., F.E.; Data Collection or Processing - M.Ç., H.Ç., G.D.A., F.E.; Analysis or Interpretation - M.Ç., H.Ç., N.S.; Literature Search - M.Ç., G.D.A.; Writing - M.Ç., H.Ç.

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Can INSM1 and Phox2B be an Alternative to Conventional Neuroendocrine Markers in the Diagnosis of Pancreatic Solid Pseudopapillary Neoplasia and Neuroendocrine Tumors?

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ABSTRACT

Introduction: Solid pseudopapillary neoplasm (SPN) and pancreatic neuroendocrine tumors (PNET) often present diagnostic challenges due to their overlapping clinical and histopathological features. We aimed to investigate the possible role of paired-like homeobox 2B (Phox2B) in this differentiation.

Methods: This study included 12 patients diagnosed with PNET and 7 patients diagnosed with SPN. Clinicopathologic data were collected and immunohistochemical staining was performed for Phox2B, synaptophysin (SYN), chromogranin-A (CHR), and insulinoma-associated protein 1 (INSM1).

Results: Phox2B exhibited limited positivity in PNET (8.3%) and rare focal staining in SPN (considered as negative). Moderate to strong immunoreactivity with SYN and CHR was observed in all PNET cases, while SPN cases showed weak to moderate SYN expression but no staining with CHR. INSM1 showed positive staining in all PNET cases and no staining in SPN cases.

Conclusion: No significant correlation was observed between Phox2B and INSM1 expressions and clinicopathologic parameters. While INSM1 serves as a reliable marker in supporting the diagnosis of neuroendocrine neoplasia in the differential diagnosis of PNET and SPN, Phox2B does not exhibit comparable diagnostic utility.

Keywords: Phox2B, solid pseudopapillary neoplasm, pancreatic neuroendocrine tumors, INSM1, synaptophysin, chromogranin-A

Introduction

Solid pseudopapillary neoplasm (SPN), first described by Frantz in 1959, is a pancreatic tumor characterized by low malignancy potential and favorable prognosis (1). Accounting for 0.9-2.7% of pancreatic neoplasms, this tumor is predominantly observed in young females (2). While pseudocystic areas with pseudopapillary structures are commonly present in SPN, some cases consist entirely of solid areas. Additionally, positive immunoreactivity for neuroendocrine markers such as synaptophysin (SYN) and CD56 necessitates differentiation from well-differentiated neuroendocrine tumors (NETs). Despite findings from electron microscopy and immunohistochemical studies, the cellular origin of SPN, whether epithelial or mesenchymal, remains to be elucidated (3-6). Therefore, the use of specific biomarkers for differentiation will offer valuable diagnostic support.

The *paired-like homeobox 2B (Phox2B*) gene, located on chromosome 4p13, is a crucial transcription factor required for the development of neural crest derivatives. It is expressed in the sympathetic and parasympathetic systems, enteric ganglia, adrenal, and extraadrenal chromaffin cells, as well as glomus cells (7,8). Additionally, the Wnt/β-catenin signaling pathway is involved in the development of neural crest-derived cells (9). Aberrant nuclear expression of β-catenin is observed in SPN and serves as an immunohistochemical marker for differential diagnosis (10,11). Phox2B, a known regulator of the autonomic nervous system and the noradrenergic system, has been utilized as a marker in the diagnosis of neoplasms such as neuroblastoma, ganglioneuroblastoma, and paraganglioma (6,12,13). These findings raise questions regarding Phox2B expression in pancreatic SPN and NETs cases, particularly concerning the potential common pathways or shared origins.

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In this study, we aimed to investigate the potential role of Phox2B in the diagnosis of pancreatic neuroendocrine tumors (PNET) and SPN, as well as its clinicopathological correlations and relationships with other immunohistochemical markers.

Methods

Sample Selection

In our pathology department, our study included 12 cases diagnosed with PNET and 7 cases diagnosed with SPN from 2014 to 2023. One PNET case was obtained through a tru-cut biopsy, while the remaining 18 cases were derived from pancreatic resection specimens, including Whipple procedures and distal pancreatectomies. Patients whose paraffin blocks could not be retrieved from the archive or who had insufficient material in the paraffin blocks were excluded from the study.

Ethical Statement

This study was approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 208, date: 18.08.2023) and was conducted in accordance with the principles of the Helsinki Declaration.

Clinical and Histopathological Evaluation

Information regarding the age, gender, tumor localization, and tumor size of the cases was extracted from the pathology reports in the hospital information system. The histological type/grade of the tumor, as well as lymphovascular and perineural invasion, was re-evaluated. Histological grading for PNET cases was conducted according to the 2019 World Health Organization Criteria for gastrointestinal system tumors (1).

Immunohistochemistry

Following the evaluation of hematoxylin- and eosin-stained slides, appropriate paraffin blocks were subjected to immunohistochemical staining for SYN, chromogranin-A (CHR), insulinoma-associated protein 1 (INSM1), and Phox2B biomarkers. Immunohistochemical reactions were performed on paraffin tissue sections using an automated immunohistochemical stainer (Ventana BenchMark ULTRA, Ventana Medical Systems, Inc., Tucson, AZ), following the manufacturer's protocol. The detection process was facilitated using the Ventana ultraVIEW DAB Detection Kit (Ventana Medical Systems, Inc.). The slides were incubated with the following primary antibodies: Phox2B [EP312](dilution 1:50, Cell Marque, Rocklin, CA, USA), INSM1 [A8] (dilution 1:100, Santa Cruz Biotechnology, Dallas, TX, USA), SYN [SP11] (dilution 1:20, Thermo Fisher Scientific, Waltham, MA, USA), and CHR [LK2H10] (ready-to-use, Ventana Medical Systems, Tucson, AZ, USA).

Evaluation of Immunohistochemistry

The immunohistochemical analysis for INSM1, Phox2B, SYN, and CHR was based on both the percentage of tumor cells exhibiting positive staining and the intensity. The extent of staining was categorized as follows: 0 (<1% stained), 1+ (1-25% stained), 2+ (26-50% stained), 3+ (51-75% stained), and 4+ (>75% stained). Staining intensity was assessed and categorized as follows: no staining (0), weak (1+), moderate (2+), or strong (3+). For INSM1, pancreatic endocrine islets served as positive controls, while a paraganglioma case was utilized as a positive control for Phox2B. Cytoplasmic staining for SYN and CHR, as well as nuclear staining for INSM1 and Phox2B, were deemed positive.

Statistical Analysis

For the statistical analysis of the data in this study, (SPSS, Chicago, IL, USA) version 26.0 was used. Descriptive statistics comprised the mean, standard deviation, median, minimum, and maximum values for continuous variables, while frequency and percentage were calculated for discrete variables. To evaluate the normality of distribution in the initial analysis, both the Kolmogorov-Smirnov and Shapiro-Wilk tests were employed. For non-parametric data between two groups, the Mann-Whitney U test and chi-square test were used. The Pearson correlation test was employed to analyze correlations between binary data. Results were evaluated within a 95% confidence interval, with a p-value of less than 0.05 considered statistically significant.

Results

The clinicopathological findings for the 19 cases, comprising 12 PNET and 7 SPN cases, are summarized in Table 1.

In one PNET case, Phox2B revealed perinuclear dot-like (Golgi zone) cytoplasmic staining (Figure 1 A, B), and, in another PNET case, Phox2B showed nuclear staining of moderate intensity, involving 50% of the tumor cells (Figure 1C). In only one of the SPN cases, sparse nuclear staining was observed in a focal area, comprising less than 1% of the tumor, thus considered negative (Figure 1D). Phox2B expression was not observed in other PNET and SPN cases.

Table 1. The clinicopathological findings of the 19 cases

	Pancreatic neuroendocrine tumor cases, (n=12)	Solid pseudopapillary neoplasm cases, (n=7)	p
Gender			1
Female	8	5	
Male	4	2	
Mean age	52	37	0.057
Tumor location			0.365
Head-uncinate process	7	2	
Body	3	2	
Tail	2	3	
Mean tumor size (cm), range (cm)	4.1 (1.5-8.5)	7.4 (3.5-18)	0.067
Lymphovascular invasion			0.326
Present	3	4	
Absent	9	3	
Perineural invasion			0.129
Present	2	4	
Absent	10	3	
Histologic grade			
Grade 1	2	-	
Grade 2	10	-	

INSM1 staining was detected in all PNET cases, exhibiting moderate to strong intensity, with the extent of expression varying from 30% to 95%. No reaction was detected in any of the SPN cases. In SPN cases, Langerhans islets, entrapped by the tumor in regions adjacent to normal pancreatic tissue, exhibited positive staining for INSM1.

Immunoreactivity with SYN was observed in all PNET and SPN cases. In PNET cases, SYN showed moderate to strong intensity and immunoreactivity, with staining extent ranging from 50% to 100%. In SPN cases, however, the expression, was weak to moderate, with staining extent ranging from 10% to 100%. No staining for CHR was observed in any of the SPN cases. In contrast, PNET cases exhibited moderate to strong intensity and expression, with staining extent ranging from 60% to 100%.

Immunohistochemical expressions of SYN, CHR, INSM1 and Phox2B, representative of most SPN cases in our study, are shown in Figure 2.

No statistically significant correlation was observed between Phox2B staining patterns in the PNET, SPN groups, and age, gender, tumor size, tumor localization, histological grade (in PNET), lymphovascular invasion, or perineural invasion.

Discussion

In recent years, with the advancement of disease-specific follow-up and treatment protocols, histopathological diagnosis has become critically important. Diagnostic procedures are increasingly being carried out using minimally invasive methods, which places pressure on pathologists to make definitive pathological diagnoses with limited material. PNET and SPN occasionally exhibit overlapping features in macroscopic, histopathological, and immunohistochemical aspects. This challenge becomes more pronounced in cytology and tru-cut biopsies. While certain immunohistochemical markers, such as CHR, E-cadherin, and β-catenin, have been reported to be useful in differential diagnosis, their roles are not well-defined (2). PNET, which originates from neuroendocrine cells derived from endodermal stem cells, expresses conventional neuroendocrine markers such as SYN, CHR, and CD56 (3). In contrast, SPN, with an unclear cellular origin, remains a subject of ongoing research (4). The absence of staining with most epithelial markers (e.g., pancytokeratin, e-cadherin) in SPN may indicate a deviation from an epithelial origin, while positivity with markers such as vimentin may suggest a mesenchymal origin (2,5). Furthermore, the frequent expression of SYN in SPN raises questions about its potential association with neuroendocrine or neural crest-derived tumors.

Phox2B is currently utilized in the diagnosis of Hirschsprung's disease and tumors of neural crest origin, such as neuroblastoma, ganglioneuroma, and paraganglioma (6). However, in NETs, the results have been inconsistent and somewhat confusing, with only a limited number of studies available. To our knowledge, no research has yet been conducted on Phox2B in SPN. Given the limited research on Phox2B, the uncertain cellular origin of SPN, and the necessity to differentiate it from PNET, these factors prompted our study.

In reviewing the literature, Phox2B positivity in paragangliomas has been reported to range from 25% to 100% (6-8). In the same studies, Lee et al. (7) and Nonaka et al. (8) did not detect Phox2B expression in any cases

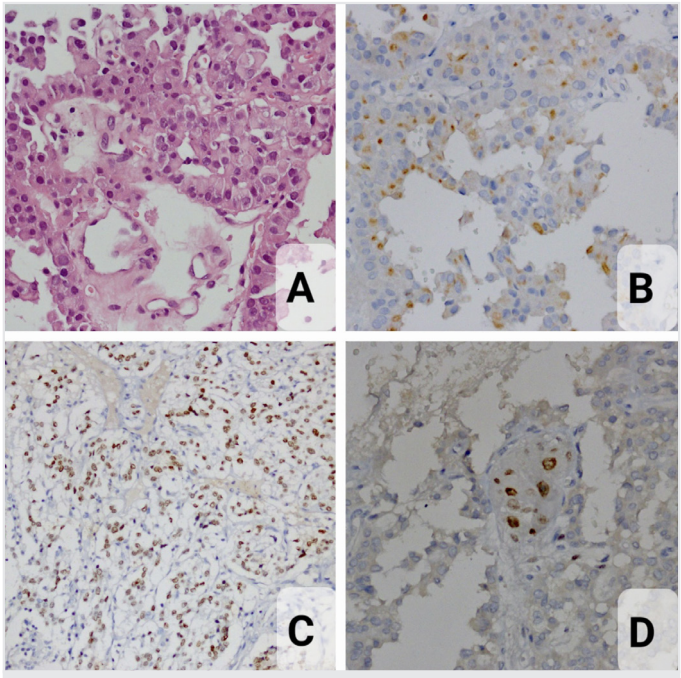

Figure 1. Phox2B staining patterns in cases of pancreatic neuroendocrine tumors and solid pseudopapillary neoplasm. [(A) Hematoxylin-eosin, x400]. The tumor shows perinuclear dot-like (Golgi zone) cytoplasmic staining for Phox2B [(B): IHC, x200]. Another PNET case showed nuclear staining with moderate intensity, accounting for 50% of cells for Phox2B [(C): IHC, x200]. One SPN case shows focal nuclear staining less than 1% of the tumor area, considered negative for Phox2B [(D) IHC, x400]
Phox2B: Paired-like homeobox 2B, IHC: Immunohistochemistry, PNET: Pancreatic neuroendocrine tumors, SPN: Solid pseudopapillary neoplasm

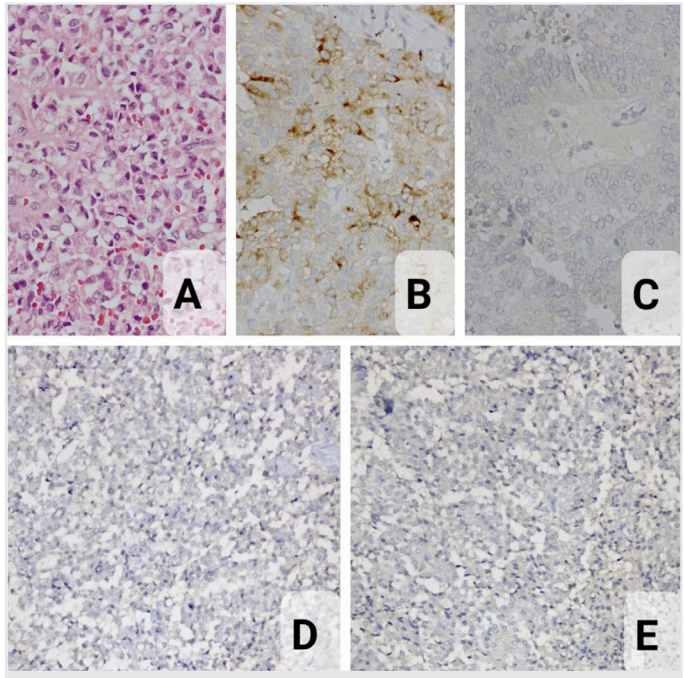

Figure 2. Solid pseudopapillary neoplasm [(A): Hematoxylin-eosin, x400]. Tumor shows patchy and moderate staining positivity for synaptophysin [(B): IHC, x400]. Chromogranin-A [(C): IHC, x400], INSM1 [(D): IHC, x200] and Phox2B [(E): IHC, x200] are negative
IHC: Immunohistochemistry, INSM1: Insulinoma-associated protein 1, Phox2B: Paired-like homeobox 2B

of NET. These studies included 15 and 67 cases of PNET, respectively. Manethova et al. (14) detected Phox2B staining in 10 of 91 NET cases but did not report any staining in the PNET cases included in their study. Of the ten cases with Phox2B expression, five were of lung origin, four were appendiceal, and one was of small intestine origin (14). On the other hand, Miyauchi et al. (12) reported immunoreactivity for Phox2B in 4 of 123 NET cases, but did not specify the origins of these NETs. In our study, moderate nuclear staining was observed in 50% of the tumor cells in one PNET case (1 out of 12 cases, or 8.3%), while perinuclear (dot-like) cytoplasmic staining was detected in another PNET case. While conflicting results regarding Phox2B expression in PNET cases have been reported in the literature, it is evident that Phox2B immunoreactivity is absent in most cases. Additionally, the antibodies, dilution ratios, and immunohistochemical methods employed in these studies vary. In our study, weak nuclear expression of Phox2B was observed in a small fraction of tumor cells (less than 1%), which was considered negative, in one case of SPN. Neither cytoplasmic nor nuclear staining was observed in other SPN cases. Due to the focal staining and the limited number of cases, interpretation remains challenging. However, it is evident that further studies with larger sample sizes are necessary to elucidate the role of Phox2B in the diagnosis of PNET and SPN.

INSM1, encoded by the *INSM1* gene, is a zinc-finger transcription factor expressed by cells undergoing terminal neuroendocrine differentiation. Originally isolated from pancreatic insulinoma and glucagonoma samples, INSM1 has been detected in various NETs, including pheochromocytoma, medullary thyroid carcinoma, pituitary tumors, small-cell lung carcinoma, and merkel cell carcinoma (15,16). INSM1 also plays a role in cell growth (17). In our study, positive staining with INSM1 was observed in all PNET cases, whereas no nuclear staining was detected in any SPN cases. Most studies in the literature have also reported positive INSM1 staining in all PNET cases (18-20). Additionally, Kim et al. (20) reported that INSM1 expression varies according to the grade of PNETs, with a decrease in INSM1 expression observed in G3 PNET cases compared to G1 and G2 PNETs. Consistent with our findings, Tanigawa et al. (18) did not detect nuclear expression of INSM1 in 5 cases of SPN; and Guo et al. (19) also reported no nuclear expression of INSM1 in 22 SPN cases. However, Tanigawa et al. (18) determined weak cytoplasmic staining in 4 of 5 cases. Additionally, Kim et al. (20) reported focal weak nuclear INSM1 staining in 5 of 14 SPN cases, while McHugh et al. (21) detected focal but strong nuclear staining in 1 of 19 cases. Although these findings may appear contradictory, the differences could be attributed to variations in antibody clones, fixation procedures, and immunohistochemical methods used. We believe that INSM1 is a strong supportive factor in the differential diagnosis of PNET and SPN, towards neuroendocrine neoplasia.

In our study, both PNET and SPN cases exhibited positive staining with SYN; however, the extent and intensity of staining varied between the two types of tumors. CHR staining was absent in all SPN cases, while positive staining was observed in all PNET cases. In the literature, SYN positivity has been reported in nearly 100% of PNET cases, whereas CHR positivity ranges between 76% and 100% (18,20,21). Similar to our study, Tanigawa et al. (18) and Kim et al. (20) reported the absence of CHR staining in SPN cases. On the other hand, McHugh et al. (21) reported CHR positivity in 3 of 15 SPN cases.

Study Limitations

Although our study's retrospective nature and limited case count are notable drawbacks, it is, to our knowledge, the first investigation specifically focusing on Phox2B in SPN cases.

Conclusion

Our study found that Phox2B did not prove useful in differentiating between PNET and SPN. On the other hand, INSM1 exhibited more specific reactions in PNET cases compared to other neuroendocrine markers such as SYN, and CHR. The complete absence of INSM1 staining in all SPN cases proved highly valuable for differential diagnosis. Particularly, for the diagnosis of SPN, we believe that further investigation with larger study cohorts is needed to elucidate the role of Phox2B.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 208, date: 18.08.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - M.C., E.Y., M.M.S.; Concept - M.C., Ö.G., C.L.; Design - M.C., Ö.G., C.L.; Data Collection or Processing - M.C., Ö.G., S.C., M.M.S.; Analysis or Interpretation - M.C., Ö.G., E.Y., C.L.; Literature Search - M.C., Ö.G., S.C., Writing - M.C., Ö.G., S.C., C.L.

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Impact of Testicular Germ Cell Tumor Laterality on Survival After Autologous Stem Cell Transplantation and High-Dose Chemotherapy

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ABSTRACT

Introduction: This study aimed to evaluate the effect of tumor localization on survival in patients undergoing autologous stem cell transplantation (ASCT), high-dose chemotherapy (HDCT) for recurrent/refractory testicular germ cell tumors (GCT).

Methods: The investigation encompassed 144 individuals with testicular germ cell cancers who had HDCT and ASCT from November 2016 to January 2024. Clinical and demographic information was retrospectively collected from the hospital's computerized database and patient records. Individuals lacking medical records and those under the age of eighteen were not included in the analysis. The study examined the clinical and demographic characteristics of the patients, overall survival (OS) following HDCT, the association between OS and tumor location, and other factors influencing OS.

Results: The median follow-up was 46.2 months. The 1-year and 3-year OS in the right testis group were 88% and 72%, respectively. The 1-year and 3-year OS in the left testis group were 70% and 56%, respectively. Although the right testis group had a better OS numerically, it was not statistically significant.

Conclusion: In this research, the impact of primary tumor lateralization on survival was evaluated in individuals having relapsed/refractory testicular GCT who had HDCT and ASCT treatment. While left testicular tumors were associated with worse numerical survival, this was primarily due to higher risk profiles in these patients. Tumor lateralization was not observed to independently impact OS.

Keywords: Testicular cancer, tumor lateralization, germ cell tumor, autologous stem cell transplantation

Introduction

The most common solid tumor in males aged 15 to 35 is testicular cancer. However, this accounts for a minimal percentage of all cancers in males, with germ cell tumors (GCT) constituting 95% of testicular cancer cases. Testicular GCTs are categorized into two distinct histopathological groups: seminoma and non-seminoma. Seminoma accounts for approximately 60% of all testicular GCT cases (1). Testicular cancer is one of the most easily treatable solid tumors with a 95% five-year survival rate (2). Despite these advances, approximately 20% of patients receiving first-line chemotherapy relapse and need salvage treatment. Salvage surgery may be conducted in individuals with anatomically limited diseases and disease recurrence (3). Nevertheless, most patients need substantial doses of salvage chemotherapy or chemotherapy. Data show that 60% of patients are cured with high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) (4). The right and left testes have different lymphatic drainage systems. The right testis drains into the vena cava, whereas the left testis drains into the left renal vein (5). Thus, the left testis is subjected to more pressure and has a slower blood flow than the right testis. It is hypothesized that the risk of systemic dissemination would be greater due to direct drainage to the heart, and lower pressure in the vascular structure of the right testis (6). In the majority of cases, tumors in the right testis tend to metastasize predominantly to the aortocaval nodes, while those in the left testis typically metastasize to the paraaortic nodes (7). There are a limited number of studies investigating the effects of primary tumor lateralization on survival. Our study aimed to determine whether tumor lateralization is a risk factor for survival in individuals with recurrent or refractory testicular GCT who had HDCT and ASCT.

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Methods

Participant selection: Male individuals with recurrent or refractory testicular germ cell cancer who had HDCT followed by ASCT and were at least 18 years old were included in this retrospective research. From November 2016 to January 2023, the investigation was carried out at University of Health Sciences Türkiye, Gülhane Training and Research Hospital's Bone Marrow Transplant Unit. Participants who qualified had undergone at least one course of platinum-based chemotherapy but experienced disease relapse. Before ASCT and intensified HDCT, they were administered induction chemotherapy with either paclitaxel, ifosfamide, and cisplatin or cisplatin, ifosfamide, and etoposide. Patients under the age of 18 or those not having accessible medical records were not included. The study comprehensively analyzed factors such as patient age, tumor histology, primary tumor location, number of metastatic sites, prior treatments, the beta-human chorionic gonadotropin (HCG) and the serum alpha-fetoprotein (AFP) values before HDCT, risk assessments based on the International Prognostic Factor Study Group (IPFSG) and International Germ Cell Cancer Collaborative Group (IGCCCG) systems, tumor response pre- and post-HDCT, overall survival (OS), and determinants influencing OS.

Chemotherapy regimens, stem cell, transplantations and endpoints: For the collection of CD34+ stem cells, a subcutaneous injection of granulocyte colony-stimulating factor at a dose of 10 mcg/kg was administered for five days. Patients received either carboplatin and etoposide (CE) or ifosfamide, carboplatin, and etoposide (ICE) HDCT regimen. Patients receiving the CE regimen were administered carboplatin (700 mg/m^2) and etoposide (700 mg/m^2) on days 1-3. Patients on the ICE regimen received ifosfamide (12 g/m^2), carboplatin (1.2 g/m^2), and etoposide (1.2 g/m^2) in 6 equal doses on days 1-6. After two days of recuperation, stem cell reinfusion was carried out. To prevent infections, all patients were given oral levofloxacin 500 mg, oral acyclovir 400 mg, and oral fluconazole 400 mg. The treatment regimen also incorporated prophylactic antiemetics and oral care products. A complete blood count was performed daily until engraftment was achieved. Platelet engraftment was defined as achieving a minimum platelet count of 20,000/mm^3 sustained for 3 consecutive days, while neutrophil engraftment was characterized by a neutrophil count reaching at least 2000/mm^3. To maintain platelet levels at 20,000/mm^3 and hemoglobin levels at 8 g/dL, platelet and erythrocyte suspensions were transfused as needed. OS, which is the investigation's main endpoint, is defined as the period between transplantation and either the patient's death or their last recorded follow-up. Radiological evaluations were conducted three months post-ASCT using positron emission tomography/computed tomography, and results were assessed with respect to RECIST 1.1 standards. A complete response (CR) was identified by the lack of active lesions that can be detected by radiography, and negative serum indicators. A 50% decrease in the sum of the longest diameters of detectable lesions or decrease more than 90% in elevated blood biomarkers were considered partial responses (PR). The absence of notable changes in tumor burden or size of lesions was defined as stable disease (SD). Increases in lesion size of over 25%, the emergence of additional lesions, or increased serum biomarker levels were indicators of progressive disease (PD).

Statistical Analysis

Statistical evaluations were performed through SPSS version 25.0. Mann-Whitney U tests and Student's t-tests were utilized to analyze independent variables. Continuous variables were presented as mean ± standard deviation, for normally distributed data, while non-normally distributed data were presented as medians. Kaplan-Meier survival analysis and log-rank tests were applied to assess cumulative survival and treatment-related correlations. Categorical variables were analyzed with chi-square and Fisher's exact tests. A p-value below 0.05 was accepted as statistically significant.

Results

The investigation involved 144 individuals. The median age at diagnosis was 32 years (18-64 years). In 77 (53.5%) patients, the primary tumor was localized in the right testis, and in 67 (46.5%), it was in the left testis. Sixteen patients (11.1%) had seminoma histology, and 128 patients (88.9%) had non-seminoma histology. Retroperitoneal lymph nodes and lungs were the most common sites of metastasis, [137 (95.1%) and 65 (45.1%) patients, respectively]. Clinicopathological features were classified based on whether they pertained to the right or left testes (Table 1). The aim was to evaluate the heterogeneity between the groups. The left testis group consisted of younger patients (p=0.02). The distribution of the two groups was normal for histological subgroups (p=0.11). When we analyzed the IPFSG and IGCCCG risk groups, we observed that the left testicular group comprised higher-risk patients (p=0.009 and p=0.001, respectively). There was no difference between metastatic sites except for lung metastases. The rate of lung metastasis was greater in the left testis group (p=0.03). No significant difference was observed in the number of metastatic sites (p=0.1). Likewise, no difference was seen between the number of lines, AFP, and beta-HCG levels before HDCT + ASCT. In the response evaluation before HDCT + ASCT, CR was seen in 22 patients (28.6%), PR in 47 patients (61%), SD in 7 patients (9.1%), and PD in 1 patient (1.3%) within the right testis group. In the left testis group, CR was seen in 13 patients (19.7%), PR in 40 patients (59.7%), SD in 11 patients (16.4%), and PD in 3 patients (4.5%). There was no difference in treatment responses among the two groups (p=0.25). Under the HDCT regimen, 138 received CE and 6 received ICE. Distribution between groups was normal (p=0.86). In the evaluation of response after HDCT + ASCT, CR was seen in 51 patients (66.2%), PR in 13 patients (16.9%), SD in 3 patients (3.9%), and PD in 10 patients (13%) in the right testicular group. In the left testis group, CR was seen in 34 individuals (50.7%), PR in 12 individuals (17.9%), SD in 8 individuals (11.9%), and PD in 13 individuals (19.4%). There were no difference in treatment responses among the 2 groups (p=0.14). No difference was seen among the groups with regard to progression status after HDCT + ASCT, but the rate of death was statistically higher in the left testis group (43% vs. 27%) (p=0.04). The median follow-up time was 46.2 months. The 1-year and the 3-year OS rates of the right testis group were 88% and 72%, respectively. One and 3-year OS rates of the left testis group were 70% and 56%, respectively. As a result of univariate analysis: non-seminoma histology (p=0.002), left testicular localization (p=0.03), IPFSG intermediate high-risk (p<0.001), IGCCCG poor risk (p<0.001), 2 or more metastatic sites (p=0.004), high AFP (p<0.001), and beta-HCG values (p<0.001) before HDCT + ASCT were linked with worse OS (Table 2). Multivariate analysis showed that the IPFSG very high-risk group (p<0.001), and AFP >1000 IU (p=0.003) before transplantation were independent variables affecting OS.

Table 1. Patient characteristics according to right and left

Patient characteristics						
n		**Right**		**Left**		**p**
		%	**n**	**%**		
Age	≤32	34	44.2	42	62.7	**0.026**
	>32	43	55.8	25	37.3	
Histology	Seminoma	12	15.6	4	6.0	0.11
	Yolk sac	4	5.2	6	9.0	
	Embryonal carcinoma	11	14.3	4	6.0	
	Choriocarcinoma	3	3.9	6	9.0	
	Teratoma	7	9.1	4	6.0	
	Mixed germ cell tumor	40	48.2	43	64.2	
IPFSG	Very low	9	11.7	2	3.0	**0.009**
	Low	22	28.6	18	26.9	
	Intermediate	27	35.1	13	19.4	
	High	9	11.7	17	25.4	
	Very high	10	13.0	17	25.4	
IGCCCG	Good	29	37.7	23	34.3	**0.001**
	Intermediate	25	32.5	7	10.4	
	Poor	23	29.9	37	55.2	
Metastatic site	Lung	29	37.7	36	53.7	0.03
	Liver	14	18.2	12	17.9	0.14
	Retroperitoneum	72	93.5	65	97.0	0.99
	Brain	4	5.2	10	14.9	0.06
	Bone	9	11.7	6	9.0	0.63
Metastatic site number	1	38	49.4	24	35.8	0.10
	≥2	39	50.6	43	64.2	
Number of treatment lines before HDCT	2	62	80.5	48	71.6	0.21
	3	8	10.4	14	20.9	
	≥4	7	9.1	5	7.5	
AFP before HDCT	<1000 IU/L	57	74.0	43	64.2	0.20
	≥1000 IU/L	20	26.0	24	35.8	
B-HCG before HDCT	<1000 IU/L	66	85.7	56	83.6	0.72
	≥1000 IU/L	11	14.3	11	16.4	
Tumor response before HDCT	CR	22	28.6	13	19.7	0.25
	PR	47	61.0	40	59.7	
	SD	7	9.1	11	16.4	
	PD	1	1.3	3	4.5	
HDCT regimen	CE	74	96.1	64	95.5	0.86
	ICE	3	3.9	3	4.5	
Tumor response after HDCT	CR	51	66.2	34	50.7	0.14
	PR	13	16.9	12	17.9	
	SD	3	3.9	8	11.9	
	PD	10	13.0	13	19.4	
Progression after HDCT	Present	43	55.8	36	46.3	0.25
	Absent	34	44.2	31	53.7	
Exitus status	Alive	56	72.7	38	56.7	0.04
	Dead	21	27.3	29	43.3	
Median follow-up time (months)	46.25					
	Right		**Left**			
1-year OS (%)	88		70			
3-years OS (%)	72		56			

IPFSG: International Prognostic Factor Study Group, IGCCCG: International Germ Cell Cancer Collaborative Group, HDCT: High-dose chemotherapy, AFP: Alpha-fetoprotein, B-HCG: Beta-human chorionic gonadotropin, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease OS: Overall survival, CE: Carboplatin and etoposide, ICE: Ifosfamide, carboplatin, and etoposide

Discussion

To date, the effect of testicular tumor laterality on survival is not known. Our study is one of the few studies investigating the effect of tumor lateralization on survival in patients with testicular GCT. In our study, we found that tumor localization did not affect OS in patients with testicular GCT who underwent HDCT + ASCT. However, the 1- and 3-year OS of patients who had right testicular tumors were numerically better (Figure 1). Similar to other solid cancers, seminomatous and non-seminomatous testicular cancers are spread by lymphatic and vascular routes (8). However, each testis has different vascular and lymphatic drainage systems. While the collecting vein of the right testicle is directly connected to the inferior vena cava, the collecting vein of the left testicle initially drains into the collecting vein of the left kidney. It is hypothesized that the left testicle is subjected to more pressure and has a relatively slower blood flow than the right testicle. There is a hypothesis that systemic spread will be higher due to direct drainage to the heart, and lower pressure in the vascular structure of the right testicle (9). Davila Dupont et al. (10) also tested this hypothesis. In a series of 37 patients by Davila Dupont et al. (10), 2-year relapse-free survival was 100% for the left testis and 77.3% for the right testis. Despite the small number of patients, the researchers showed that there was a tendency for earlier relapse in right testicular GCTs (10). The study by Yıldız et al. (11) is among the few studies investigating laterality in testicular GCTs. In their study, the patients with left testicular tumors had improved survival outcomes. However, HDCT + ASCT was performed in a small number of patients. Although the patient population in the compared study was larger than ours, most of the participants were early-stage. The number of high-risk patients was significantly lower than anticipated in our study. Only 40 patients underwent HDCT + ASCT (11). Miao et al. (12) studied the effect of tumor laterality on survival in 1213 individuals with diffuse large B-cell lymphoma (DLBCL) of testicular origin. Although no significant effect of laterality on survival was demonstrated, both

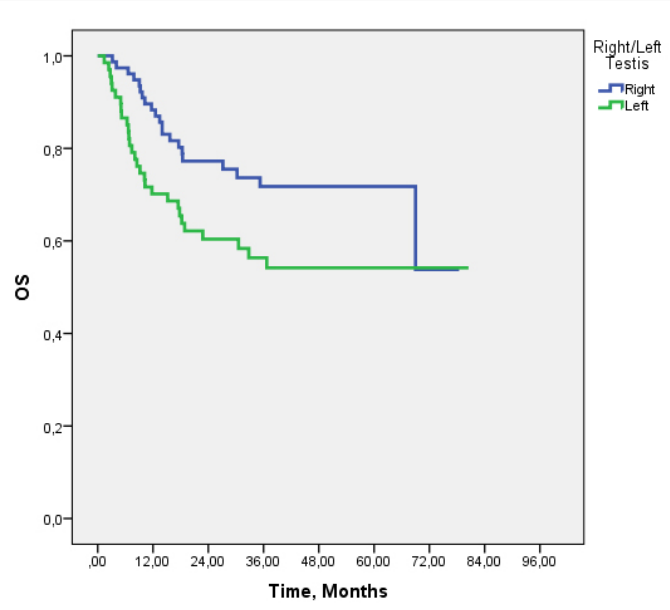

Figure 1. Kaplan-Meier curves for overall survival-tumor lateralization relationship
OS: Overall survival

Table 2. Analysis of patiens for OS according to clinicopathological factors

		Median OS (months) univariate	p	HR (95% CI) multivariate	p
Age	≤32	69.0	0.581		
	>32	NR			
Histology	Seminoma	NR	0.023	0.60 (0.07-4.72)	0.63
	Non-seminoma	59.0			
Localization	Right	NR	0.030	1.25 (0.70-2.24)	0.44
	Left	NR			
Metastatic site number	1	NR	0.004	1.17 (0.58-2.33)	0.65
	≥2	69.0			
IPFSG	Very low	NR	<0.001	2.04 (1.47-2.83)	<0.001
	Low	NR			
	Intermediate	69.0			
	High	NR			
	Very high	9.0			
IGCCCG	Good	NR	<0.001	1.19 (0.81-1.74)	0.37
	Intermediate	NR			
	Poor	30.5			
AFP	<1000 IU/L	NR	<0.001	2.37 (1.33-4.25)	0.003
	≥1000 IU/L	18.6			
HCG	<1000 IU/L	NR	<0.001	1.68 (0.88-3.22)	0.11
	≥1000 IU/L	14.0			

IPFSG: International Prognostic Factor Study Group, IGCCCG: International Germ Cell Cancer Collaborative Group, AFP: Alpha-fetoprotein, HCG: Human chorionic gonadotropin, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, NR: Not reached

10-year cancer-specific survival and OS were better in the left testis group (12). In a study by Gundrum et al. (13) in 769 individuals with testicular DLBCL, left testicular origin was shown to be a poor prognostic factor. This was the largest study in the literature that showed results similar to ours. There are a limited number of studies in the scientific community investigating the effect of testicular tumor lateralization on survival, and the results are contradictory. In our study, the survival of the left testis group was numerically worse, but this difference was not statistically significant. The main reason for this is thought to be that the left testicular group consisted of higher risk patients. When both IPFSG and IGCCCG risk scores are analyzed, it is evident that the left testis group has a higher risk. Many studies have shown that IPFSG and IGCCCG scores are important in determining prognosis (14,15). In our study, both IPFSG and AFP >1000 IU were found to be independent variables for OS.

Study Limitations

Our investigation has some limitations. In addition to being single-center and retrospective, our patient population is relatively small.

Conclusion

In conclusion, our study included 144 patients who underwent HDCT + ASCT. All patients were metastatic and had experienced recurrence. Although there are articles supporting the early recurrence of right testicular tumors, there are few studies on survival, and the two most significant studies were on testicular DLBCL. The results of these two studies contradict each other. Our paper describes one of the largest cohorts investigating the effect of lateralization on OS in patients with testicular GCT, and it found no effect of testicular tumor lateralization on survival. Since all our patients received HDCT + ASCT treatment, performing this study on a rare group increases its value. Further studies with larger patient populations are needed to confirm these findings and better understand the role of tumor laterality in testicular cancer prognosis.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee (approval number: 2024-215, date: 24.04.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Concept - A.T., B.K., N.K.; Design - A.T., A.D., E.K.T.; Data Collection or Processing - Ö.F.K., E.K.T., G.A.; Analysis or Interpretation - A.T., B.K., N.M., G.A.; Literature Search - A.T., A.D., Ö.F.K., N.M.; Writing - A.T., G.A., N.K.

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Evaluation of Frailty Levels in Hemodialysis Patients

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ABSTRACT

Introduction: This study aimed to investigate the relationship between: the etiology of chronic renal failure (CRF), hemodialysis duration, body mass index, residual renal function (RRF), ultrafiltration volume, dialysis dose value, and frailty levels by utilizing laboratory values and patient-related data from individuals undergoing hemodialysis due to CRF.

Methods: A total of 56 patients, comprising 22 females and 34 males, undergoing hemodialysis treatment due to CRF, were included in the study. Patients with active infections, hepatitis B, hepatitis C, human immunodeficiency virus, acute renal failure, or chronic liver disease were excluded. Frailty levels were assessed through a questionnaire based on the Frailty Scale and the Edmonton Frailty Scale.

Results: Frailty levels were found to be higher in patients with diabetes mellitus, cardiovascular disease (CVD), and peripheral arterial disease (PAD) compared to those without these conditions ($p=0.003$, $p=0.000$, $p=0.035$, respectively). In patients with severe anemia (hemoglobin<10), frailty levels were also higher ($p=0.024$). No significant relationship was found between the patients' age, dialysis duration (in years), calcium, phosphorus, uric acid, parathyroid hormone, RRF, and the clinical frailty index averages, ($p\geq0.05$).

Conclusion: In patients undergoing hemodialysis due to CRF. Diabetes mellitus, CVD, PAD, and anemia are factors that contribute to increased frailty. In patients receiving hemodialysis for CRF, well-conducted hemodialysis treatment can be considered effective in preventing frailty. Anemia is a treatable factor, and its management may be associated with a reduction in frailty and cardiovascular mortality.

Keywords: Chronic renal failure, hemodialysis treatment, clinical frailty index

Introduction

Chronic renal failure (CRF) is a progressiveloss of renal function that most often develops secondary to systemic diseases. It is generally seen as a consequence of conditions such as diabetes mellitus, hypertension, and glomerulonephritis, and it is characterized by deterioration of nephrons with an irreversible loss of function. A diagnosis is established when the glomerular filtration rate falls below 60 mL/minimum/1.73 m² for a duration of at least three months, accompanied by a progressive decline in renal function. CRF may also exert secondary effects on metabolism and the endocrine system. It can cause fluid retention, electrolyte disturbances (such as hyperkalemia and hyponatremia), acid-base imbalances, and the accumulation of urea and creatinine. Additionally, it can secondarily lead to various systemic complications, including anemia, hypertension, bone turnover disorders, and cardiovascular diseases (CVD). These effects exacerbate the overall condition of patients and significantly impair their quality of life. Early diagnosis is crucial for slowing the progression of CRF, enhancing patients' quality of life, and preventing potential complications. Furthermore, the treatment methods employed play a crucial role in preserving renal function and preventing further deterioration. Treatment strategies may vary depending on the patient's general condition, renal function, underlying diseases in the etiology, and individual characteristics. Timely interventions can extend survival and slow disease progression, thereby facilitating better management of the condition.

Frailty is a condition frequently observed in the elderly, though it can occur in any age group, especially in the context of chronic illnesses. CRF can impair physical capacity, thereby increasing frailty. In this context, frailty can be defined as an increased susceptibility of the body to stress, both psychologically and physiologically. Individuals with CRF may be more vulnerable to such stressors, which need to be addressed seriously, as they can complicate the treatment process (1,2). The Frail Scale is frequently used as a screening method in the assessment of frailty (3). Frailty, which progressively increases due to chronic diseases and aging, manifests with symptoms such as involuntary weight loss, weakness, fatigue, reduced physical activity, and a decline in walking speed. Malnutrition and impaired psychosocial status are also among the factors that contribute to the development of frailty. When assessing the frailty status of patients, these factors should be considered collectively, as they can lead to falls, hospitalizations, prolonged illness, and loss of independence. Therefore, early recognition of frailty symptoms and

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timely interventions are crucial for preserving and enhancing quality of life (4). As people get older, their frailty increases. Fragility becomes more prevalent in individuals over 65, and it becomes even more pronounced in those over 85. It is essential to take preventive measures in such cases (5). Another scale used to assess frailty in the geriatric population is the study of osteoporotic fractures index, which predicts the risks of falls, disability, fractures, and mortality. It can be valuable in clinical practice for identifying frailty in elderly patients who are at risk of adverse health outcomes (6). In hospitalized patients, the Edmonton Frail Scale (EFS) is more commonly used. This scale encompasses various aspects, including cognition, general health status, functionality, social support, medication use, nutrition, mood, physical performance, and incontinence (7). Compared to individuals with normal renal function, patients with CRF are significantly more prone to frailty (8,9). Frailty levels are notably higher in patients undergoing hemodialysis and are associated with increased mortality and morbidity, and exceed that of CRF patients who have not yet started dialysis (10).

Methods

Patients

This study included a total of 56 patients, comprising 22 females and 34 males. The patients included in the study were individuals who had been receiving hemodialysis treatment two or three times a week for at least three months due to end-stage renal disease. Patients with active infections, including hepatitis B virus, hepatitis C virus, human immunodeficiency virus, acute renal failure, or chronic liver disease, were excluded from the study. The clinical frailty index was assessed using the EFS in a questionnaire format, and the frailty levels of the patients were evaluated. The study was approved by the Scientific Research Ethics Committee of Kocaeli City Hospital (approval number: 2024-112, date: 26.09.2024). Consent forms were obtained from all patients.

Statistical Analysis

Data analysis was conducted using GraphPad Prism 9.5.0 and IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics for the patient group variables were presented as frequencies and percentages for categorical variables, and as Mean ± SD deviation or median (interquartile range) for continuous variables. The data were assessed for normality; for comparisons between two independent groups, either the Independent Samples t-test or the Mann-Whitney U test was employed, and chi-square (χ^2) analysis was used for categorical variables. A p-value of <0.05 was considered statistically significant.

Results

A total of 56 patients were included in the study, consisting of 22 females (39.3%) and 34 males (60.7%). The age range of the patients was 27 to 80 years, with a mean age of 62.26 years. Patients had been receiving hemodialysis for an average duration of 3.64 years, with a range from 1 to 11 years (Table 1).

According to the results of our study, frailty levels were higher, although not statistically significant, in patients aged 65 and older. Frailty levels were significantly higher in patients with diabetes mellitus, CVD, and peripheral arterial disease (PAD) compared to those without these conditions (p=0.003, p=0.000, and p=0.035, respectively) (Figure 1). No statistically significant relationship was found between the ultrafiltration volume (UF) in each session, residual renal function (RRF) or body mass index (BMI) (p≥0.05) (Table 2).

In patients with severe anemia [hemoglobin (Hb)<10], frailty levels were also found to be statistically significant higher (p=0.024) (Figure 2). No statistically significant relationship was found between the average clinical frailty levels and patients' age, duration of hemodialysis treatment (in years), or laboratory values, including CRP, ferritin, parathyroid hormone, serum albumin, potassium, phosphorus, calcium, uric acid and dialysis dose (Kt/V), (p≥0.05) (Table 3).

Table 1. Descriptive statistics of patient variables

Variables	Mean ± SD	Median (IQR)
Age (years)	62.73±13.06	66.00 (17.75)
HD years	3.54±2.44	3.00 (2.00)
UF (mL)	2589.95±881.46	2900.00 (1400.00)
CRP (mg/L)	21.53±45.98	6.70 (13.20)
Ferritin (ng/mL)	471.76±340.99	395.00 (310.05)
PTH (pg/mL)	482.88±401.54	377.85 (329.50)
Hb (g/dL)	10.43±1.69	10.70 (2.52)
Albumin (g/dL)	3.71±0.48	3.71 (0.54)
K (mmoL/L)	5.02±0.64	5.06 (0.91)
P (mg/dL)	4.96±1.38	5.15 (2.22)
Ca (mg/dL)	8.74±0.76	8.65 (1.20)
Uric acid (mg/dL)	5.78±1.03	5.80 (1.25)
Kt/V daugirdas	1.60±0.20	1.57 (0.36)
RRF (mL/day)	311.70±322.35	200.00 (500.00)
CFI	4.05±1.61	4.00 (2.00)
BMI (kg/m^2)	26.82±5.83	25.15 (8.96)

HD: Hemodialysis duration, UF: Ultrafiltration, CRP: C-reactive protein, PTH: Parathyroid hormone, Hb: Hemoglobin, K: Potassium, P: Phosphorus, Ca: Calcium, Kt/V: Dialysis dose, RRF: Renal residual function, CFI: Clinical frailty index, BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range

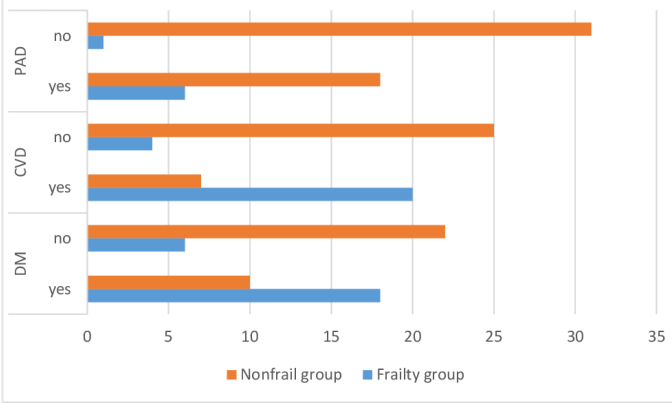

Figure 1. The relationship between frailty and DM, CVD, and PAD in hemodialysis patients

DM: Diabetes mellitus, CVD: Cardiovascular disease, PAD: Peripheral arterial disease

Discussion

This study evaluated the laboratory values and clinical data of hemodialysis patients with end-stage renal failure. In particular, the relationships of laboratory values, causes of renal failure, duration of hemodialysis, BMI, RRF, UF volume, and Kt/V values, with the patients' frailty levels were evaluated. As individuals age, their health status and functional capacities become increasingly vulnerable. They emphasize the importance of recognizing frailty in older adults and developing strategies to prevent falls (11). It has been observed that the prevalence of PAD increases after the age of 60, along with a corresponding rise in frailty levels (12). In our study, although not statistically significant, higher frailty levels were observed in patients aged 65 and older (n=33). It has been emphasized that diabetes mellitus leads to a complication such as frailty, which is associated with chronic inflammation (13). Shauyet et al. (14) reported that frailty increases the risk of hypoglycemia in elderly diabetic patients, while Meneilly et al. (15) emphasized that elderly diabetic patients are more prone to frailty. The results indicate that the presence of diabetes mellitus in the etiology of CRF is a significant factor contributing to increased frailty throughout the course of the disease. Having diabetes mellitus in the patient increases the risk of CVD, leading to a higher incidence of frailty (16). In our study, frailty levels were higher in the hemodialysis patient group with diabetes compared to those without diabetes. The incidence of CVD also increases in patients with CRF (17,18). Frailty may serve as both a consequence of CVD and a determining factor in its development and progression. This suggests that frail individuals are at risk regarding heart health and may face an increased risk of future heart disease in addition to their current health issues (19). In patients over 70 years of age who underwent percutaneous revascularization, those with frailty syndrome had a higher mortality rate compared to those without frailty (20). Yalınkılıç et al. (21) reported that frailty levels in elderly patients with heart failure were moderate. However, our study found high frailty levels in hemodialysis patients with CVD. In patients with CRF, the presence of PAD can be associated with serious outcomes, including balance disorders, falls, hospitalizations, and even death (12). According to the findings of this study, frailty levels were significantly higher in hemodialysis patients with PAD.

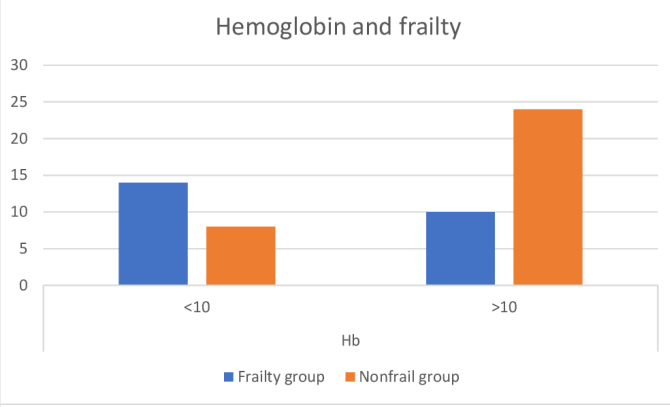

Figure 2. The relationship between hemoglobin levels and frailty in hemodialysis patients

Anemia, which manifests with symptoms such as weakness, palpitations, and fatigue, can significantly reduce an individual's daily functional capacity, adversely affecting both physical and mental performance. Anemia and frailty are two prevalent conditions in the elderly, both of which are associated with increased morbidity and mortality (22). Mutlay and Seydi (23), found, utilizing the Fried Frailty Scale, that frailty scores were significantly higher in individuals with anemia compared to other groups. This finding highlights the negative impact of anemia on overall health and its contribution to increased frailty levels. Low Hb levels in the elderly have been recognized as an independent risk factor for the development of frailty (24). Within the scope of this research, hemodialysis patients with severe anemia (Hb<10), demonstrated a statistically significant increase in frailty scores compared to those with Hb levels above 10 (12). Çelebi et al. (25) indicated that hypoalbuminemia and reduced urine output are independent risk factors for frailty.

Table 2. Relationship between clinical frailty index and variables

Clinical Frailty Index (CFI)						
		Non-frail	Frail	χ^2	SD	p
Gender	Female	13	9	0.056	1	0.813
	Male	19	15			
Etiology	DM	10	18	8.823	1	0.003
	Other	22	6			
CVD	No	25	4	18.358	1	0.000
	Yes	7	20			
PAD	No	31	18	6.306	1	0.035
	Yes	1	6			
BMI (kg/m^2)	<18.50	1	1	0.239	2	0.887
	18.80-25	14	9			
	≥25	17	14			
RRF (mL/day)	<200	12	14	1.629	1	0.202
	≥200	20	10			
UF (mL)	<2000	7	8	0.427	1	0.514
	≥2000	25	16			

DM: Diabetes mellitus, CVD: Cardiovascular disease, PAD: Peripheral arterial disease, BMI: Body mass index, RRF: Renal residual function, UF: Ultrafiltration, SD: Standard deviation

Table 3. Relationship between clinical frailty index and variables

Clinical Frailty Index (CFI)						
		Non-frail	Frail	χ^2	SD	p
Albumin (g/dL)	<3.50 ≥3.50	5 27	7 17	0.798	1	0.372
CRP (mg/L)	<5 ≥5	16 16	9 15	0.435	1	0.510
Hb (g/dL)	<10 ≥10	8 24	14 10	5.068	1	**0.024**
K (mmol/L)	<5.1 ≥5.1	19 13	12 12	0.182	1	0.670
Ca (mg/dL)	<8.5 ≥8.5	8 24	10 14	1.066	1	0.302
P (mg/dL)	<4.50 ≥4.50	11 21	11 13	0.351	1	0.554
PTH (pg/mL)	<240 ≥240	9 23	5 19	0.097	1	0.755
Ferritin (ng/mL)	<100 ≥100	1 31	1 23	0.043	1	0.835
Uric acid (mg/dL)	<6.1 ≥6.1	19 13	16 8	0.078	1	0.780
Kt/V	<1.60 ≥1.60	5 27	1 23	0.875	1	0.223

CRP: C-reactive protein, Hb: Hemoglobin, K: Potassium, Ca: Calcium, P: Phosphorus, PTH: Parathyroid hormone, Kt/V: Dialysis dose, SD: Standard deviation

However, in the present study, no significant correlation was observed among albumin levels, RRF, and frailty. Some findings in the current literature suggest that the impact of hypoalbuminemia and RRF on frailty in patients with CRF undergoing hemodialysis warrants further evaluation in larger study populations. This may be in contrast to other findings. Consequently, further research in this area is needed. No significant correlation was found between the frailty score and serum CRP levels, a result that does not support the anticipated relationship between frailty and inflammation. Similarly, no significant association was observed between the frailty score and parameters such as Kt/V or applied UF, suggesting that the effectiveness of hemodialysis treatment and UF does not negatively impact frailty. The patients' age, BMI, dialysis duration (in years), and levels of PTH, calcium, phosphorus, and uric acid were also not found to be significantly associated with frailty.

Study Limitations

The limitations of this study include the limited number of patients, the cross-sectional design, and the inclusion of patients from a specific region.

Conclusion

Patients with CKD undergoing hemodialysis are characterized by increased frailty, which can be attributed to factors such as DM, CVD, PAD, and anemia. The presence of DM in the etiology of CRF constitutes a significant factor contributing to the increased frailty observed throughout the disease progression. Moreover, the concomitant presence of cardiovascular and PAD significantly exacerbates frailty, while anemia, a common comorbidity in these patients, represents a modifiable risk factor. Correcting anemia may help reduce the heightened risk of frailty. The absence of an effect of the other evaluated parameters on frailty in patients could be due to the effectiveness of hemodialysis treatment. Long-term, consistent, and well-managed hemodialysis can result in improvements in both hemodynamic and biochemical parameters, thus reducing frailty and minimizing the detrimental effects associated with CRF. As a result, this can decrease the risk of potential complications, promote sustained overall well-being, and delay the progression of frailty. Furthermore, monitoring the frailty index and implementing appropriate preventive and corrective measures are essential for reducing cardiovascular morbidity and mortality.

Ethics

Ethics Committee Approval: The study was approved by the Scientific Research Ethics Committee of Kocaeli City Hospital (approval number: 2024-112, date: 26.09.2024).

Informed Consent: Consent forms were obtained from all patients.

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

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